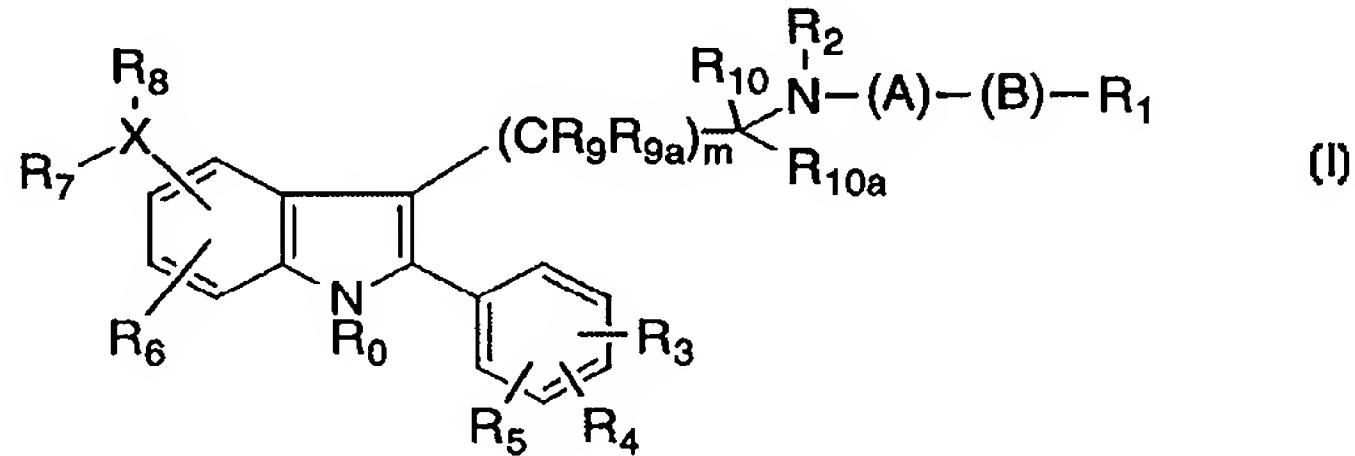




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(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		Published With international search report.	
(72) Inventors; and (75) Inventors/Applicants (for US only): GOULET, Mark [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). UJ-JAINWALLA, Feroze [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WALSH, Thomas, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WYVRATT, Matthew, J., Jr. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			

(54) Title: ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE



(57) Abstract

There are disclosed compounds of formula (I) and pharmaceutically acceptable salts thereof which are useful as antagonists of GnRH and as such may be useful for the treatment of a variety of sex-hormone related and other conditions in both men and women.

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TITLE OF THE INVENTION

ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE

BACKGROUND OF THE INVENTION

5 The gonadotropin-releasing hormone (GnRH), also referred to as luteinizing hormone-releasing hormone (LHRH), is a decapeptide that plays a key role in human reproduction. The hormone is released from the hypothalamus and acts on the pituitary gland to stimulate the biosynthesis and secretion of luteinizing hormone (LH) and follicle-
10 stimulating hormone (FSH). LH released from the pituitary gland is primarily responsible for the regulation of gonadal steroid production in both sexes, whereas FSH regulates spermatogenesis in males and follicular development in females. GnRH agonists and antagonists have proven effective in the treatment of certain conditions which require
15 inhibition of LH/FSH release. In particular, GnRH-based therapies have proven effective in the treatment of endometriosis, uterine fibroids, polycystic ovarian disease, precocious puberty and several gonadal steroid-dependent neoplasia, most notably cancers of the prostate, breast and ovary. GnRH agonists and antagonists have also been utilized in
20 various assisted fertilization techniques and have been investigated as a potential contraceptive in both men and women. They have also shown possible utility in the treatment of pituitary gonadotrophe adenomas, sleep disorders such as sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hyperplasia, hirsutism,
25 as an adjunct to growth hormone therapy in growth hormone deficient children, and in murine models of lupus.

 Current GnRH antagonists are GnRH-like decapeptides which are generally administered intravenously or subcutaneously presumably because of negligible oral activity. These have amino acid substitutions usually at positions one, two, three, six and ten.

 Non-peptide GnRH antagonists offer the possible advantage of oral administration. Non-peptide GnRH antagonists have been described in European Application 0 219 292 and in De, B. et al., J. Med. Chem., **32**, 2036-2038 (1989), in WO 95/28405, WO 95/29900 and EP 0679642
35 all to Takeda Chemical Industries, Ltd.

Substituted indoles known in the art include those described in the following patents and patent applications. US Patent No. 5,030,640 discloses alpha-heterocyclic ethanol aminoalkyl indoles which are potent β -agonists. US Patent No. 4,544,663 discloses indolamine derivatives which are allegedly useful as male anti-fertility agents. WO 90/05721 discloses alpha-amino-indole-3-acetic acids useful as anti-diabetic, anti-obesity and anti-atherosclerotic agents. French patent 2,181,559 discloses indole derivatives with sedative, neuroleptic, analgesic, hypotensive, antiserotonin and adrenolytic activity. Belgian patent 879381 discloses 3-aminoalkyl-1H-indole-5-thioamide and carboxamide derivatives as cardiovascular agents used to treat hypertension, Raynaud's disease and migraine. WO 97/21435, WO 97/21703, WO 97/21707 and WO 97/21704 disclose non-peptidyl, indole derivatives as GnRH antagonists.

15

SUMMARY OF THE INVENTION

The present invention relates to compounds which are non-peptide antagonists of GnRH which can be used to treat a variety of sex-hormone related conditions in men and women, to methods for their preparation, and to methods and pharmaceutical compositions containing said compounds for use in mammals.

Because of their activity as antagonists of the hormone GnRH, the compounds of the present invention are useful to treat a variety of sex-hormone related conditions in both men and women. 25 These conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as cancers of the prostate, breast and ovary, gonadotrophe pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. 30 They are also useful as an adjunct to treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosis. Further, the compounds of the invention may be useful in *in vitro* fertilization and as contraceptives. The compounds may also be useful in combination with androgens, estrogens, progesterones, 35 antiestrogens and antiprogestogens for the treatment of endometriosis,

fibroids and in contraception. They may also be useful in combination with testosterone or other androgens or antiprogestogens in men as a contraceptive. The compounds may also be used in combination with an angiotensin-converting enzyme inhibitor such as Enalapril or Captopril,
5 an angiotensin II-receptor antagonist such as Losartan or a renin inhibitor for the treatment of uterine fibroids. Additionally, the compounds of the invention may also be used in combination with bisphosphonates (bisphosphonic acids) and other agents, such as growth hormone secretagogues, e.g. MK-0677, for the treatment and prevention
10 of disturbances of calcium, phosphate and bone metabolism, in particular, for the prevention of bone loss during therapy with the GnRH antagonist, and in combination with estrogens, progestones, antiestrogens, antiprogestins and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes
15 during therapy with the GnRH antagonist.

Additionally, a compound of the present invention may be co-administered with a 5a-reductase 2 inhibitor, such as finasteride or epristeride; a 5a-reductase 1 inhibitor such as 4,7b-dimethyl-4-aza-5a-cholestan-3-one, 3-oxo-4-aza-4,7b-dimethyl-16b-(4-chlorophenoxy)-5a-androstane, and 3-oxo-4-aza-4,7b-dimethyl-16b-(phenoxy)-5a-androstane as disclosed in WO 93/23420 and WO 95/11254; dual inhibitors of 5a-reductase 1 and 5a-reductase 2 such as 3-oxo-4-aza-17b-(2,5-trifluoromethylphenyl-carbamoyl)-5a-androstane as disclosed in WO 95/07927; antiandrogens such as flutamide, casodex and cyproterone acetate, and alpha-1 blockers such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin.
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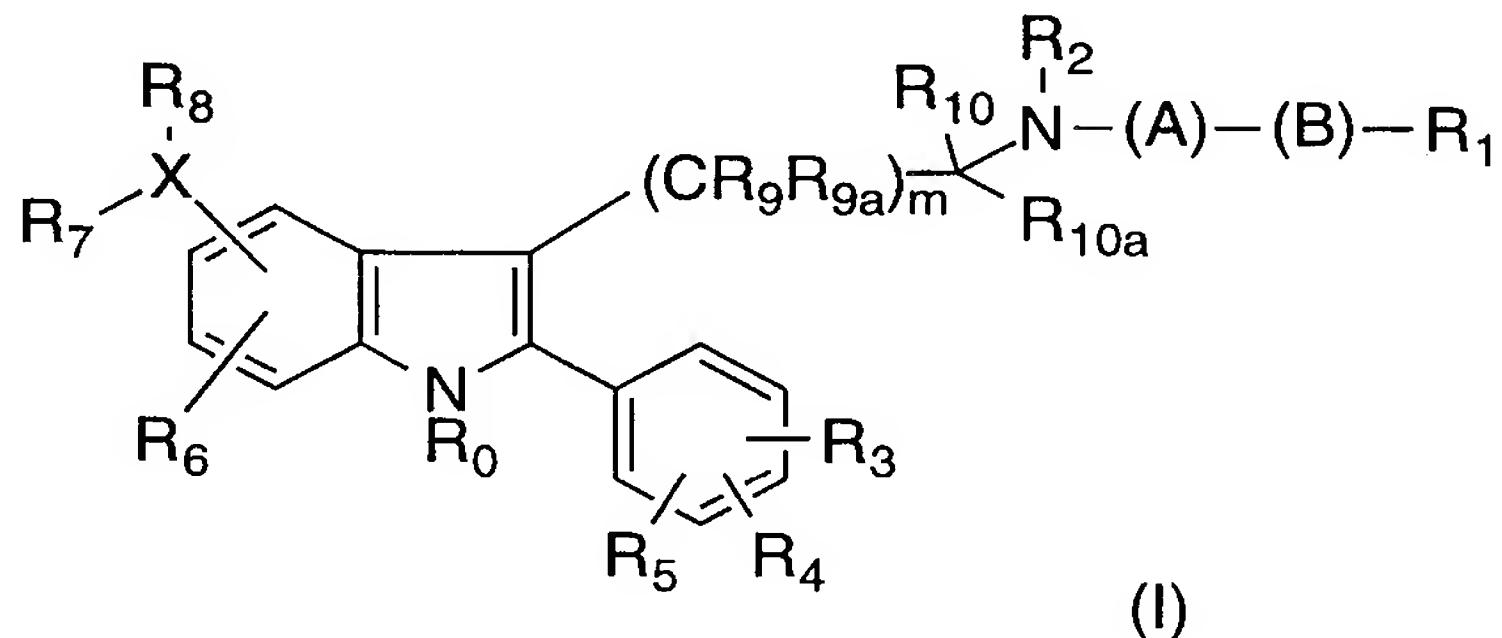
Further, a compound of the present invention may be used in combination with growth hormone, growth hormone releasing hormone or growth hormone secretagogues, to delay puberty in growth
30 hormone deficient children, which will allow them to continue to gain height before fusion of the epiphyses and cessation of growth at puberty.

Further, a compound of the present invention may be used in combination or co-administered with a compound having luteinizing hormone releasing activity such as a peptide or natural
35 hormone or analog thereof. Such peptide compounds include

leuprorelin, gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterlin and recirelin.

DETAILED DESCRIPTION OF THE INVENTION

5 The present invention relates to compounds of the general formula

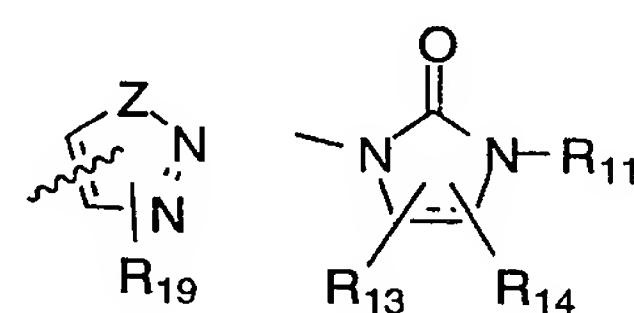
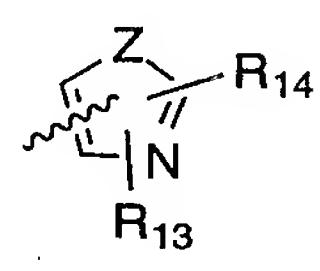
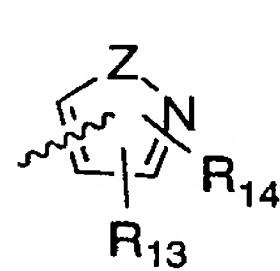
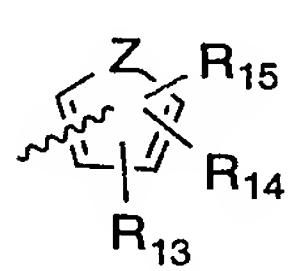
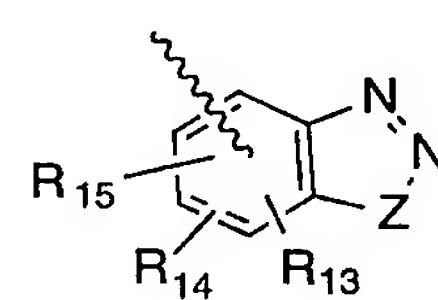
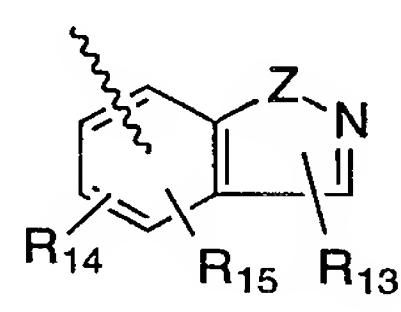
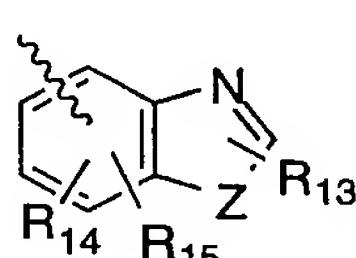
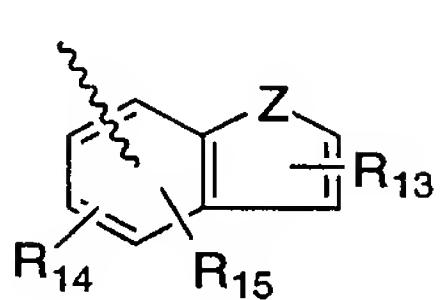


wherein

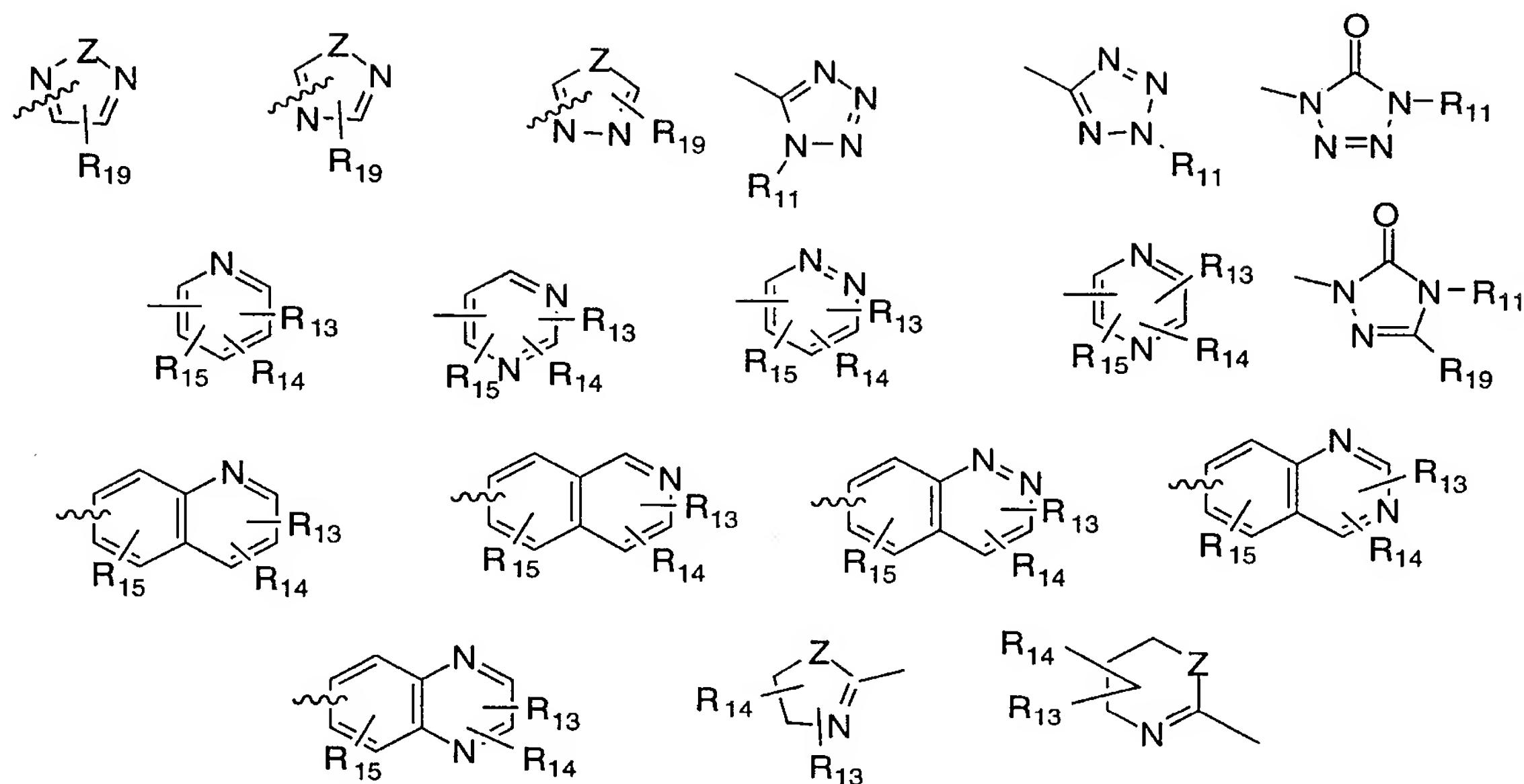
10 A is R22-[heteroaryl]-R22- or R22-[substituted heteroaryl]-R22-;
 B is optionally absent, -OR22-, -C(=O)R22-, -S(O)nR22-,
 -NR18R22-, -OC(=O)R22-, -C(=O)OR22, -OS(O)nR22- or
 -S(O)nOR22-;

15 R0 is hydrogen, C1-C6 alkyl, substituted C1-C6 alkyl, wherein the substituents are as defined below; aryl, substituted aryl, aralkyl or substituted aralkyl, wherein the substituents are as defined for R3, R4 and R5;

R1 is



20



the nitrogen atoms contained in the R₁ heteroaromatic rings may exist either as drawn or, when chemically allowed, in their oxidized (N→O) state;

5 R₂ is heteroaryl, substituted heteroaryl, C₁-C₆ heteroaralkyl, C₁-C₆ substituted heteroaralkyl; or

10 R₂ is A-B-R₁; or

10 R₂ and A can optionally be taken together to form a ring of 5-7 atoms;

10 R₃, R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, CN, nitro, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, aryl, substituted aryl, aralkyl, substituted aralkyl, R₁₁O(CH₂)_p-, (CH₂)_pS(O)_nR₁₇ or halogen; wherein R₁₇ is hydrogen,

15 C₁-C₆ alkyl, C₁-C₃ perfluoroalkyl, aryl or substituted aryl; or

15 R₃ and R₄ taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing 1-3 heteroatoms selected from N, O and S;

20 R₆ is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, C₁-C₃ perfluoroalkyl, CN, NO₂, halogen, R₁₆O(CH₂)_p;

20 R₇ is hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl, unless X is hydrogen or halogen, then R₇ is absent;

R₈ is hydrogen, C(O)OR₉, C(O)NR₁₁R₁₂, NR₁₁R₁₂, C(O)R₁₁,
 NR₁₂C(O)R₁₁, NR₁₂C(O)NR₁₁R₁₂, NR₁₂S(O)₂R₁₁,
 NR₁₂S(O)₂NR₁₁R₁₂, OC(O)R₁₁, OC(O)NR₁₁R₁₂, OR₁₁,
 SOnR₁₁, S(O)_nNR₁₁R₁₂,, a heterocyclic ring or bicyclic
 5 heterocyclic ring with from 1 to 4 heteroatoms selected from
 N, O or S which can be optionally substituted by R₃, R₄ and
 R₅, C₁-C₆ alkyl or substituted C₁-C₆ alkyl, unless X is
 hydrogen or halogen, then R₈ is absent; or

R₇ and R₈ taken together form a heterocyclic ring containing one or
 10 more heteroatoms selected from N, O or S which can be
 optionally substituted by R₃, R₄ and R₅; or

R₇ and R₈ taken together form a carbocyclic ring of 3-7 atoms or $\text{O} \parallel$
 15 when m \neq 0;
 R₉ and R_{9a} are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆
 alkyl; aryl or substituted aryl, aralkyl or substituted aralkyl
 when m \neq 0; or

R₉ and R_{9a} taken together form a carbocyclic ring of 3-7 atoms or $\text{O} \parallel$
 20 when m \neq 0;
 R₁₀ and R_{10a} are independently hydrogen, C₁-C₆ alkyl, substituted C₁-
 C₆ alkyl, aryl, substituted aryl, aralkyl or substituted
 aralkyl; or

R₁₀ and R_{10a} taken together form a carbocyclic ring of 3-7 atoms or $\text{O} \parallel$;
 25 R₉ and R₁₀ when taken together form a carbocyclic ring of 3-7 carbon
 atoms or a heterocyclic ring containing one or more
 heteroatoms when m \neq 0; or

R₉ and R₂ taken together form a heterocyclic ring containing 3-7 carbon
 atoms and one or more heteroatoms when m \neq 0; or

R₁₀ and R₂ taken together form a heterocyclic ring containing 3-7 carbon
 atoms and one or more heteroatoms;

R₁₁ and R₁₂ are independently a bond, hydrogen , C₁-C₆ alkyl,
 30 substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl,

5 substituted aralkyl, a carbocyclic ring of 3-7 atoms, a substituted carbocyclic ring containing 3-7 atoms, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅, C₁-C₆-alkyl substituted by a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅;

10 R₁₁ and R₁₂ when taken together can form an optionally substituted ring of 3-9 atoms;

15 R₁₃ is hydrogen, OH, NR₇R₈, NR₁₆SO₂(C₁-C₆ alkyl), NR₁₆SO₂(substituted C₁-C₆ alkyl), NR₁₆SO₂(aryl), NR₁₆SO₂(substituted aryl), NR₁₆SO₂(C₁-C₃ perfluoroalkyl); SO₂NR₁₆(C₁-C₆ alkyl), SO₂NR₁₁(substituted C₁-C₆ alkyl), SO₂NR₁₁(aryl), SO₂NR₁₆(substituted aryl), SO₂NR₁₆(C₁-C₃ perfluoroalkyl); SO₂NR₁₆(C(O)C₁-C₆ alkyl); SO₂NR₁₆(C(O)-substituted C₁-C₆ alkyl); SO₂NR₁₆(C(O)-aryl); SO₂NR₁₆(C(O)-substituted aryl); S(O)_n(C₁-C₆ alkyl); S(O)_n(substituted C₁-C₆ alkyl), S(O)_n(aryl), S(O)_n(substituted aryl), C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, C₁-C₆ alkoxy, substituted C₁-C₆ alkoxy, COOH, halogen, NO₂ or CN;

20 R₁₄ and R₁₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, CN, nitro, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, aryl, substituted aryl, aralkyl, substituted aralkyl, R₁₆O(CH₂)_p-, R₁₆C(O)O(CH₂)_p-, R₁₆OC(O)(CH₂)_p-, -(CH₂)_pS(O)_nR₁₇, -(CH₂)_pC(O) N(R₁₆)₂ or halogen; wherein R₁₇ is hydrogen, C₁-C₆ alkyl, C₁-C₃ perfluoroalkyl, aryl or substituted aryl;

25 R₁₆ is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic ring of 3-7 atoms or a substituted carbocyclic ring containing 3-7 atoms;

30 R₁₈ is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C(O)OR₁₆, C(O)N(R₁₆)₂, C(O)R₁₆, S(O)_nR₁₆;

35

R₁₉ is either the definition of R₁₃ or R₁₄;

R₂₂ is C₀-C₄ alkyl, substituted C₁-C₄ alkyl;

X is N, O, S(O)_n, C(O), (CR₁₁R₁₂)_p, a single bond to R₈, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; when X is O, S(O)_n, C(O), or CR₁₁R₁₂ only R₈ is possible;

5 Z is O, S or NR₁₁;

m is 0, 1, 2 or 3;

n is 0, 1 or 2;

10 p is 0, 1, 2, 3 or 4; and the alkyl, cycloalkyl, alkenyl and alkynyl substituents are selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, hydroxy, oxo, cyano, C₁-C₆ alkoxy, fluoro, C(O)OR₁₁, aryl C₁-C₃ alkoxy, substituted aryl C₁-C₃ alkoxy, and the aryl substituents are as defined for R₃, R₄ and R₅;

15 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

20 In a preferred embodiment, there are disclosed compounds of formula I wherein

A is R₂₂-[thiophene]-R₂₂-;

R₀ is hydrogen;

25 R₁ is

the nitrogen atoms contained in the R₁ heteroaromatic rings may exist either as drawn or, when chemically allowed, in their oxidized (N→O) state;

30 R₃, R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl or halogen;

R₈ is C(O)NR₁₁R₁₂, or

R₁₁ and R₁₂ are independently a bond, hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic ring of 3-7 atoms, a substituted carbocyclic ring containing 3-7 atoms, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅, C₁-C₆-alkyl substituted by a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅;

5 R₁₁ and R₁₂ when taken together can form an optionally substituted ring of 3-9 atoms;

10 X is (CR₁₁R₁₂)_p;

15 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

20 Preferred substituents when R₁₁ and R₁₂ are taken together include 7-aza-bicyclo[2.2.1]heptane and 2-aza-bicyclo[2.2.2]octane.

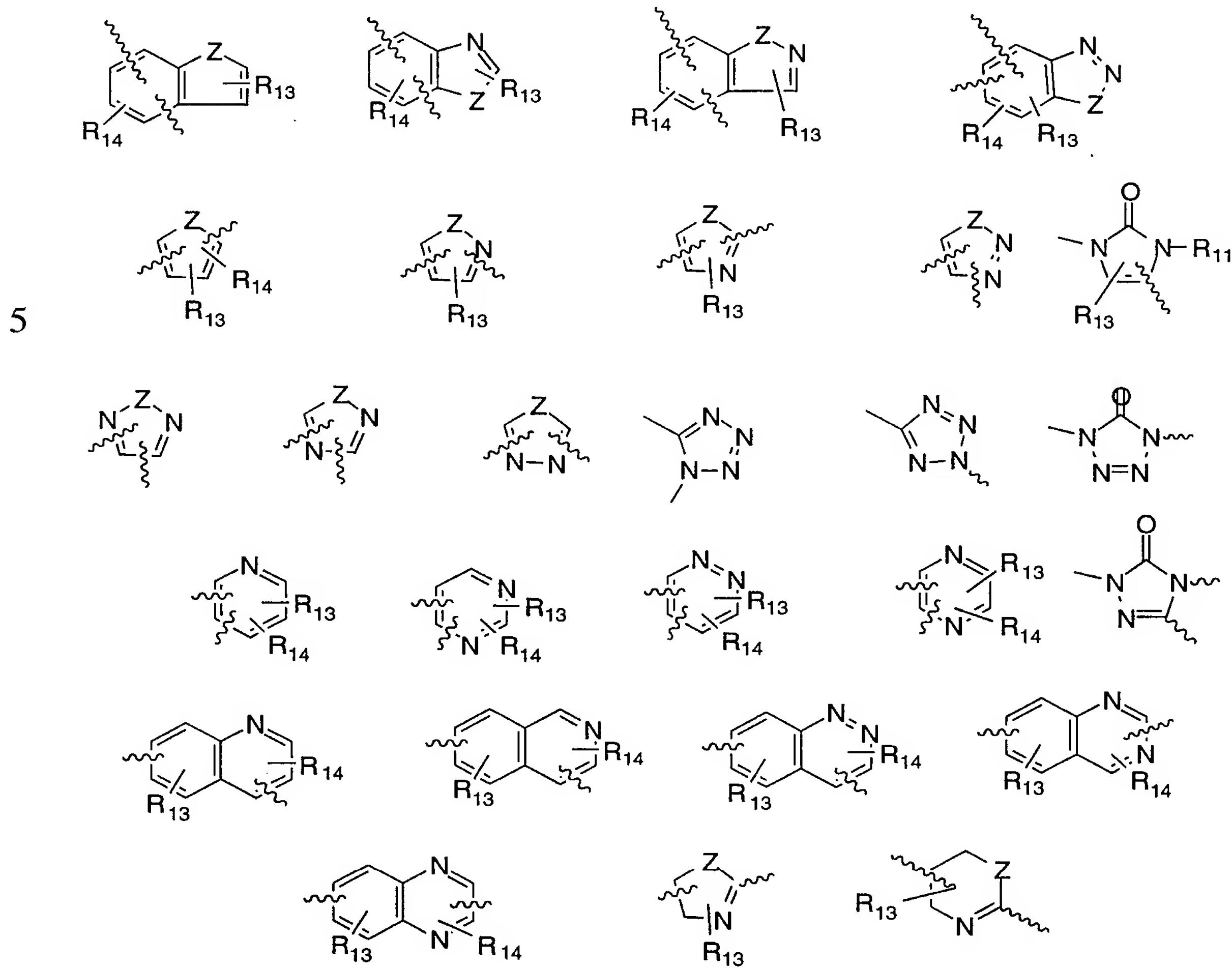
Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and claims.

25 When any variable (e.g., aryl, heterocycle, R₁, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

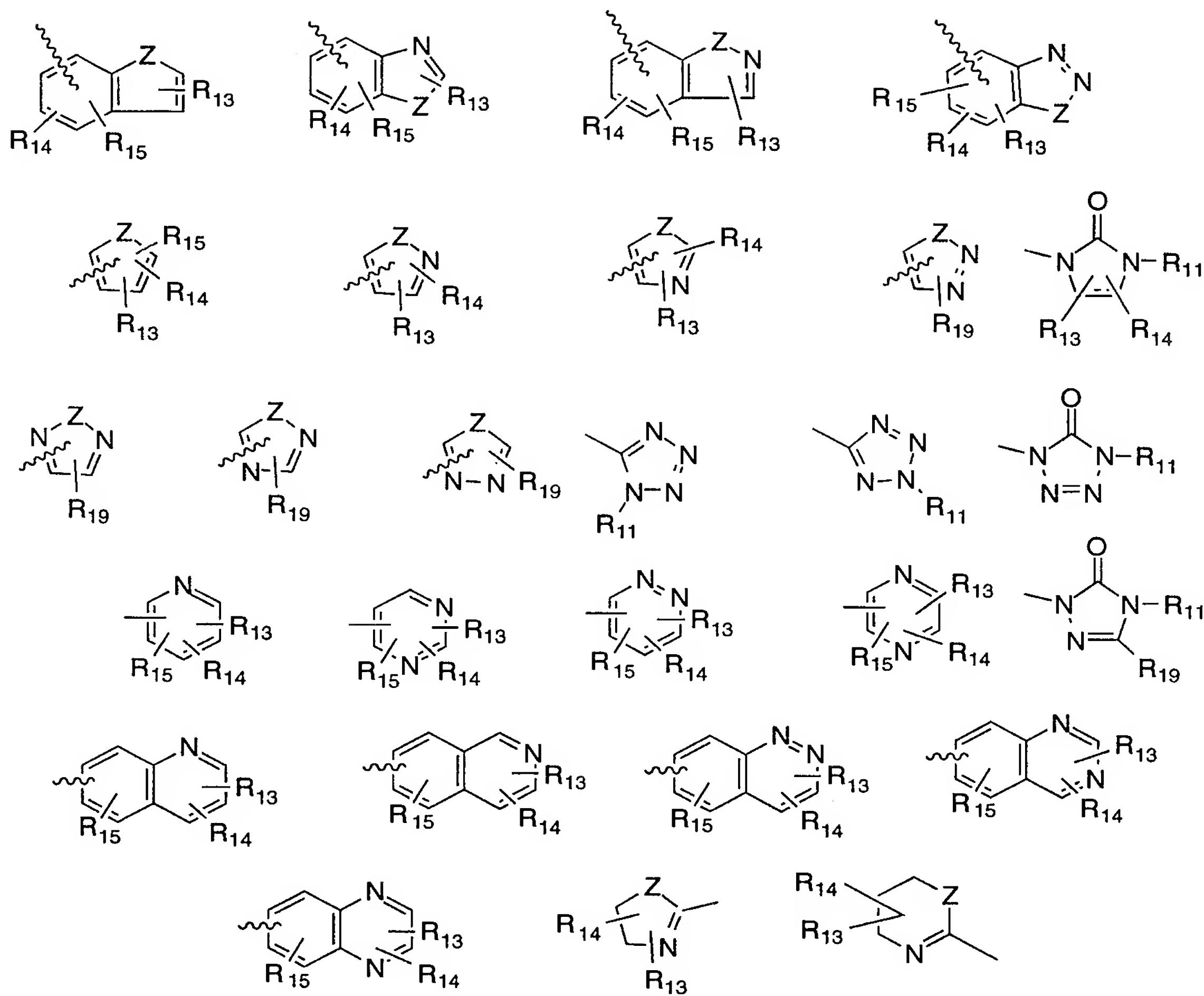
30 The term "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, e.g., methyl (Me), ethyl (Et), propyl, butyl, pentyl, hexyl, heptyl, octyl, nonanyl, decyl, undecyl, dodecyl, and the isomers thereof such as isopropyl (i-Pr), isobutyl (i-Bu), sec-butyl (s-Bu), tert-butyl (t-Bu), isopentane, isohexane, etc.

The term "aryl" includes phenyl and naphthyl. Preferably, aryl is phenyl.

The term "heteroaryl" is intended to include the compounds shown below:



where Z is O, S, or NR₁₁, as well as the following compounds:



The term "halogen" or "halo" is intended to include
5 fluorine, chlorine, bromine and iodine.

The term "heterocycle" or "heterocyclic ring" is defined by all non-aromatic, heterocyclic rings of 3-7 atoms containing 1-3 heteroatoms selected from N, O, and S, such as oxirane, oxetane, tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, 10 tetrahydropyridine, tetrahydropyrimidine, tetrahydrothiophene, tetrahydrothiopyran, morpholine, hydantoin, valerolactam, pyrrolidinone, and the like.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or

indirectly, from combination of the specified ingredients in the specified amounts.

5 In addition, it is well known to those skilled in the art that many of the foregoing heterocyclic groups can exist in more than one tautomeric form. It is intended that all such tautomers be included within the ambit of this invention.

10 The optical isomeric forms, that is mixtures of enantiomers, e.g., racemates, or diastereomers as well as individual enantiomers or diastereomers of the instant compound are included. These individual enantiomers are commonly designated according to the optical rotation they effect by the symbols (+) and (-), (L) and (D), (1) and (d) or combinations thereof. These isomers may also be designated according to their absolute spatial configuration by (S) and (R), which stands for sinister and rectus, respectively.

15 The individual optical isomers may be prepared using conventional resolution procedures, e.g., treatment with an appropriate optically active acid, separating the diastereomers and then recovering the desired isomer. In addition, the individual optical isomers may be prepared by asymmetric synthesis.

20 Additionally, a given chemical formula or name shall encompass pharmaceutically acceptable addition salts thereof and solvates thereof, such as hydrates.

25 The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility and other desirable properties.

30 The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" is intended to include all acceptable salts. Examples of acid salts are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or 35 can be used in sustained release or prodrug formulations. Depending

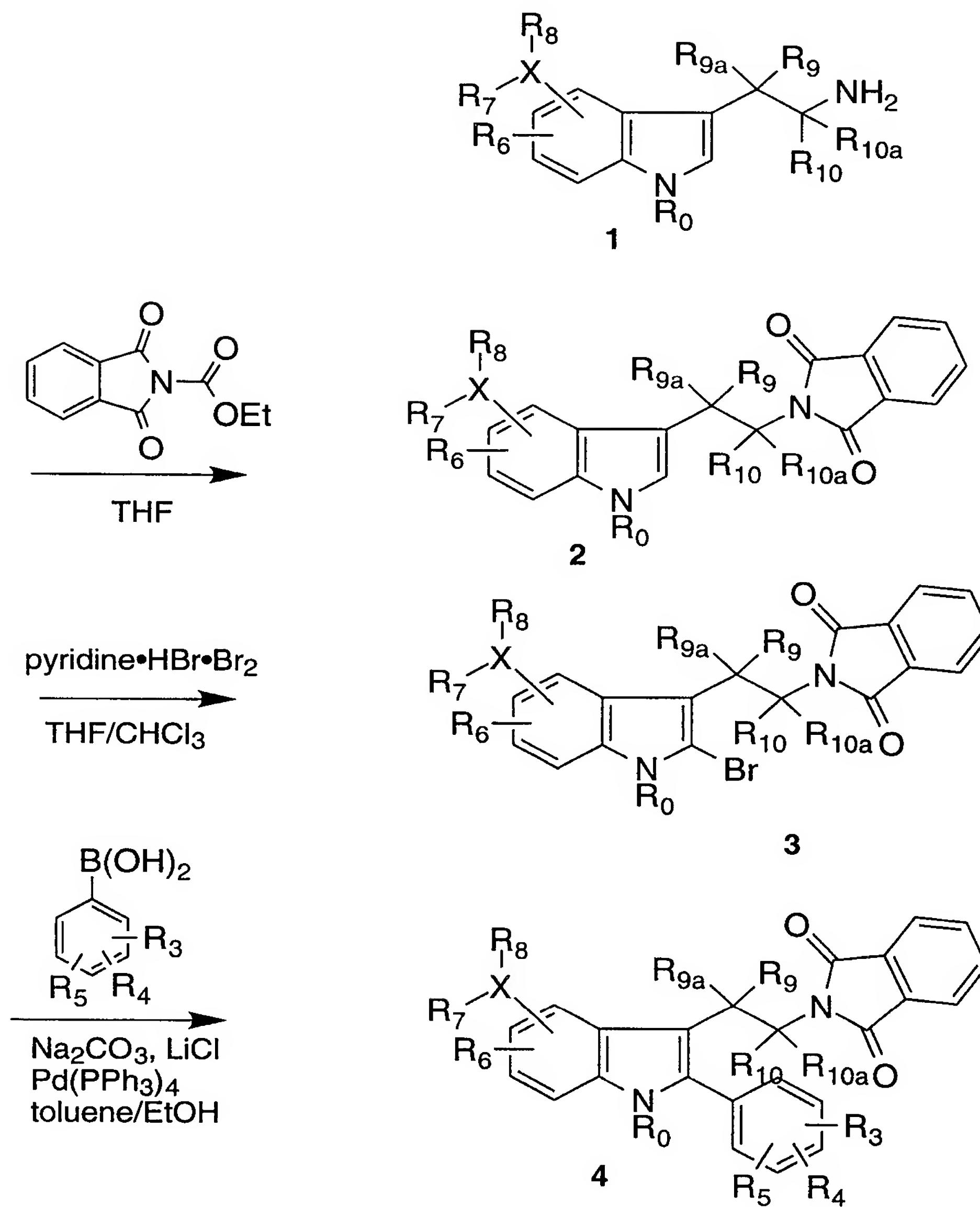
on the particular functionality of the compound of the present invention, pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such 5 as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethyl-10 ammonium hydroxide. These salts may be prepared by standard procedures, e.g. by reacting a free acid with a suitable organic or inorganic base, or alternatively by reacting a free base with a suitable organic or inorganic acid.

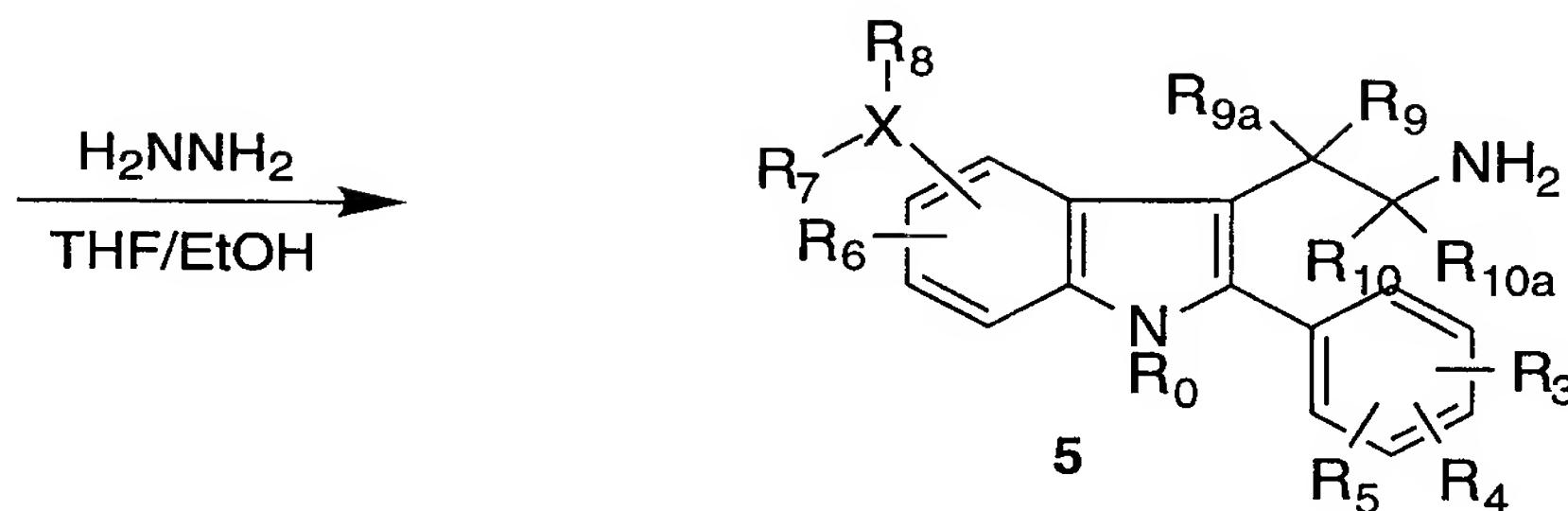
Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed, e.g. 15 methyl, ethyl, butyl, acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

The compounds of the present invention may have chiral centers other than those centers whose stereochemistry is depicted in 20 formula I, and therefore may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers, with all such isomeric forms being included in the present invention as well as mixtures thereof. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and 25 as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

The compounds of the invention are prepared by the 30 following reaction schemes. All substituents are as defined above unless indicated otherwise.

Scheme A



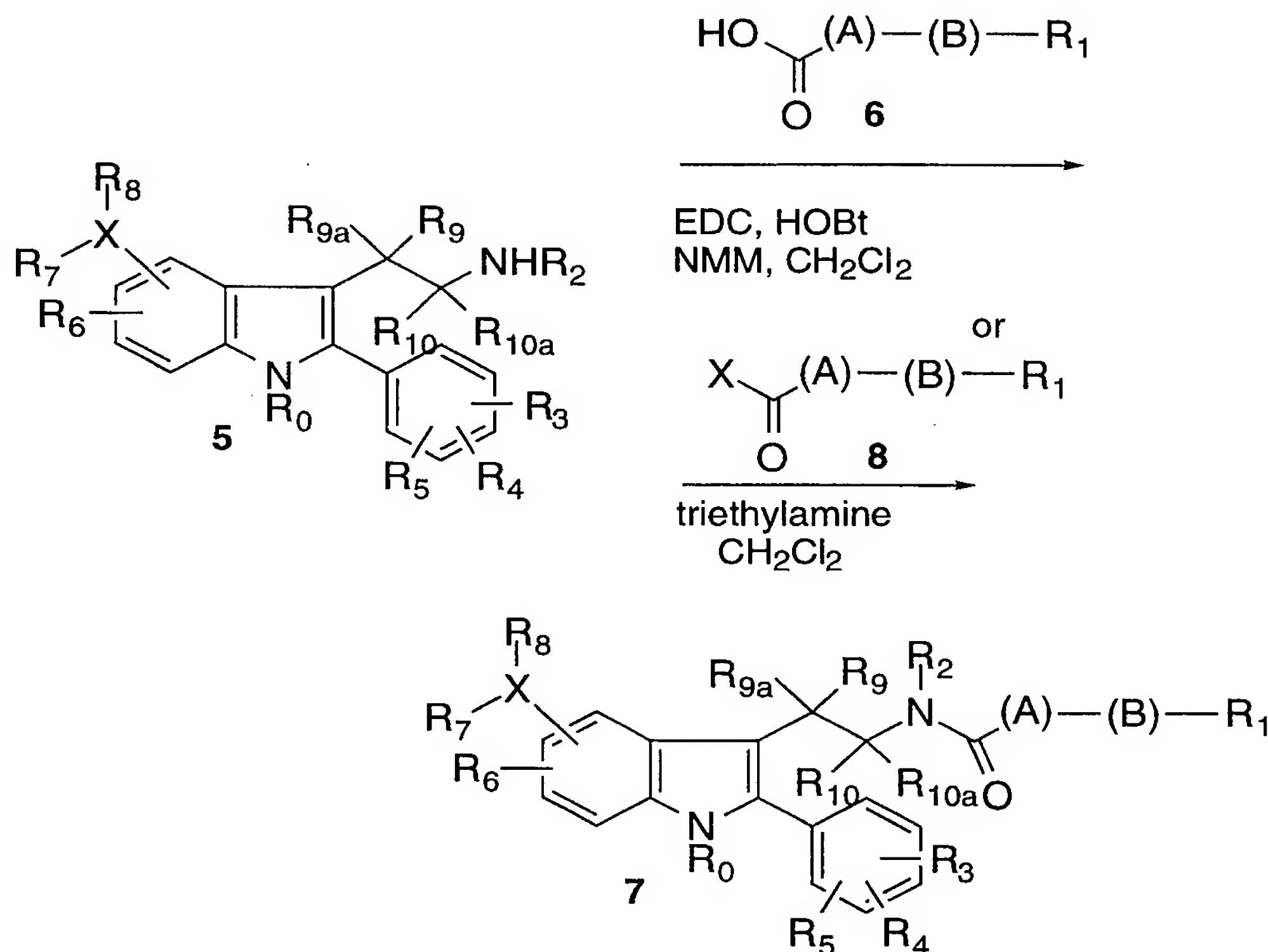


Reaction Scheme A

As shown in reaction Scheme A, treatment of tryptamine

5 (1) with *N*-carboxyphthalimide in an inert organic solvent such as tetrahydrofuran at a temperature of 20-65°C, preferably 65°C, for a period of 12-48 hours gives the corresponding *N*-phthalimidotryptamine derivative (2). The *N*-phthalimidotryptamine (2) could be further modified by treatment with a brominating agent such as pyridinium
 10 hydrobromide perbromide, pyrrolidone hydrotribromide, or the like in an inert organic solvent such as tetrahydrofuran, methylene chloride, chloroform, or mixtures thereof at 0-25°C for a period of 30 minutes to 4 hours to provide the 2-bromotryptamine (3). Bromide (3) may be reacted with an arylboronic acid (prepared essentially as described in :
 15 Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.-H. *Chem. Scr.* **1986**, *26*, 311-314.) with palladium (0) catalysis, a weak base such as aqueous sodium carbonate or the like, and a chloride source such as lithium chloride in an inert solvent like toluene, benzene, ethanol, propanol or mixtures thereof at a temperature of 25°-100°C, preferably 80°C, for a period of
 20 1-6 hours to give the 2-aryltryptamine derivative (4). Finally, the phthalimido group may be removed by treatment of (4) with aqueous hydrazine in an inert solvent such as methanol or ethanol at a temperature of 0°-25°C for a period of 4-24 hours to give tryptamine (5).

Scheme B

Reaction Scheme B

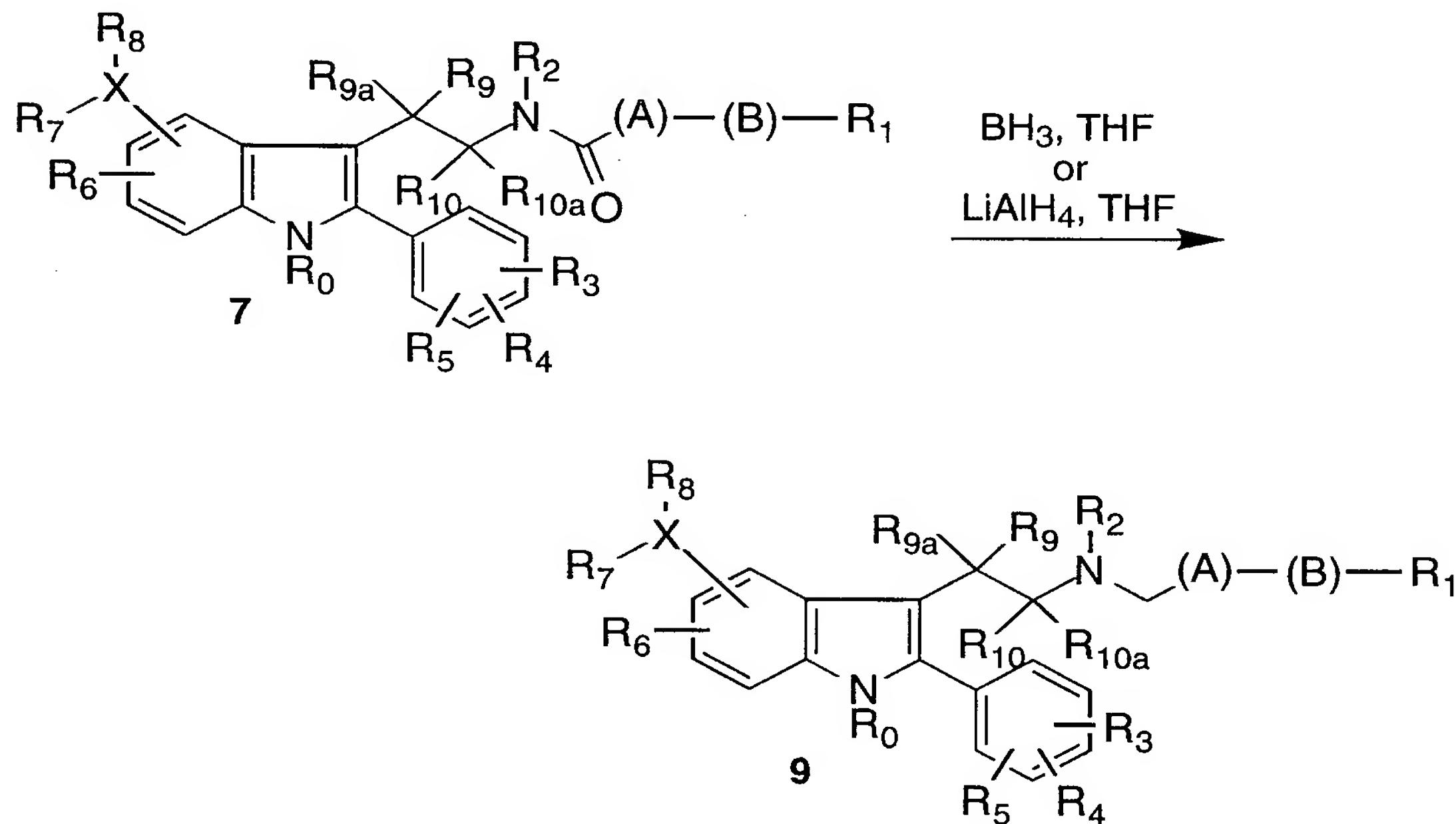
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As shown in reaction Scheme B, the 2-aryltryptamine may be condensed with a carboxylic acid of type (6) using the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or the like with or without 10 1-hydroxybenzotriazole (HOBT) and a tertiary amine base such as N-methylmorpholine (NMM), triethylamine or the like in an inert organic solvent such as methylene chloride, chloroform, dimethylformamide, or mixtures thereof at or near room temperature for a period of 3-24 hours to provide the corresponding amide derivative (7). Alternatively, 2-15 aryltryptamine (5) can be treated with an active ester or acid chloride of type (8) in an inert organic solvent such as methylene chloride, chloroform, tetrahydrofuran, diethyl ether, or the like and a tertiary

amine base such as triethylamine, diisopropylethylamine, pyridine or the like at a temperature of 0°-25°C for 30 minutes to 4 hours to give (7).

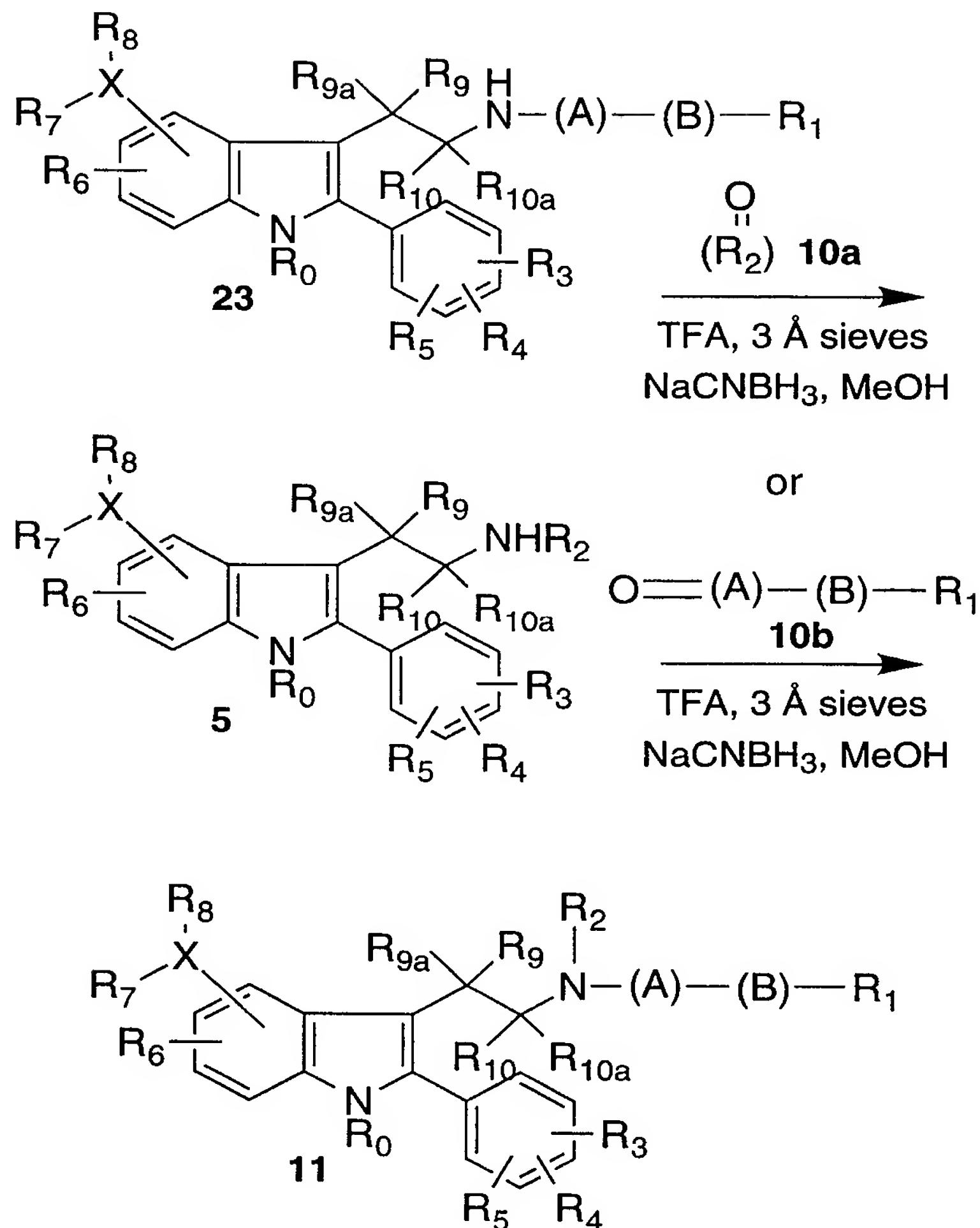
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Scheme C

Reaction Scheme C

10 As shown in reaction Scheme C, the amide carbonyl of (7) can be reduced by treatment with borane, lithium aluminum hydride, or equivalent hydride sources in an inert organic solvent such as tetrahydrofuran, diethyl ether, 1,4-dioxane or the like at 25°-100°C, preferably 65°C, for a period of 1-8 hours to give the corresponding amine 15 compound (9).

Scheme D



5

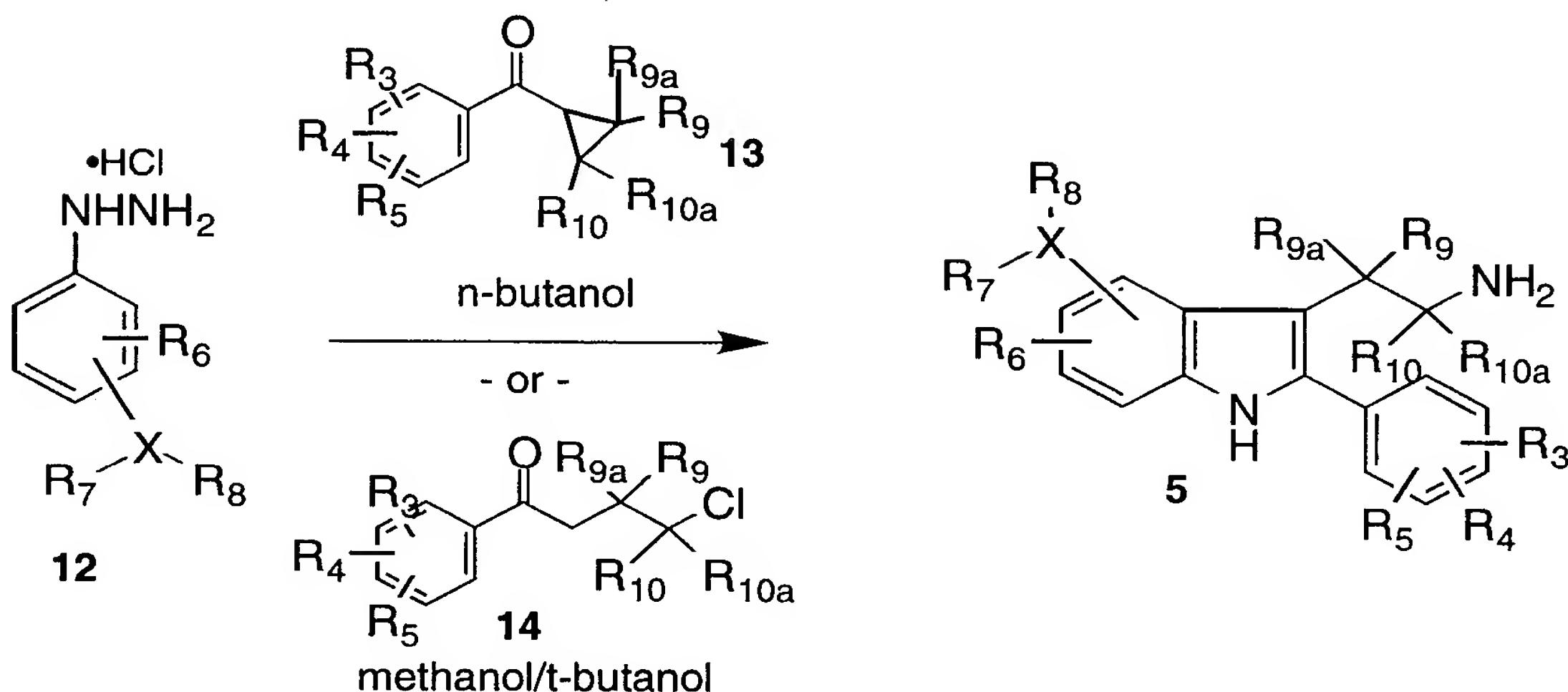
Reaction Scheme D

As shown in reaction Scheme D, the 2-aryltryptamine (23 or 5) can be modified by treatment with an aldehyde or ketone of type (10a or 10b) in the presence of a weak acid such as trifluoroacetic acid (TFA), 10 acetic acid or the like, with or without a dessicant such as 3 Å molecular sieves or magnesium sulfate, and a hydride source such as sodium borohydride or sodium cyanoborohydride, in an inert organic solvent such as methanol, ethanol, isopropanol, tetrahydrofuran, dichloromethane, chloroform, or mixtures thereof at a temperature of

0°-25°C for a period of 1-12 hours to give the corresponding secondary or tertiary amine derivative (11).

Scheme E

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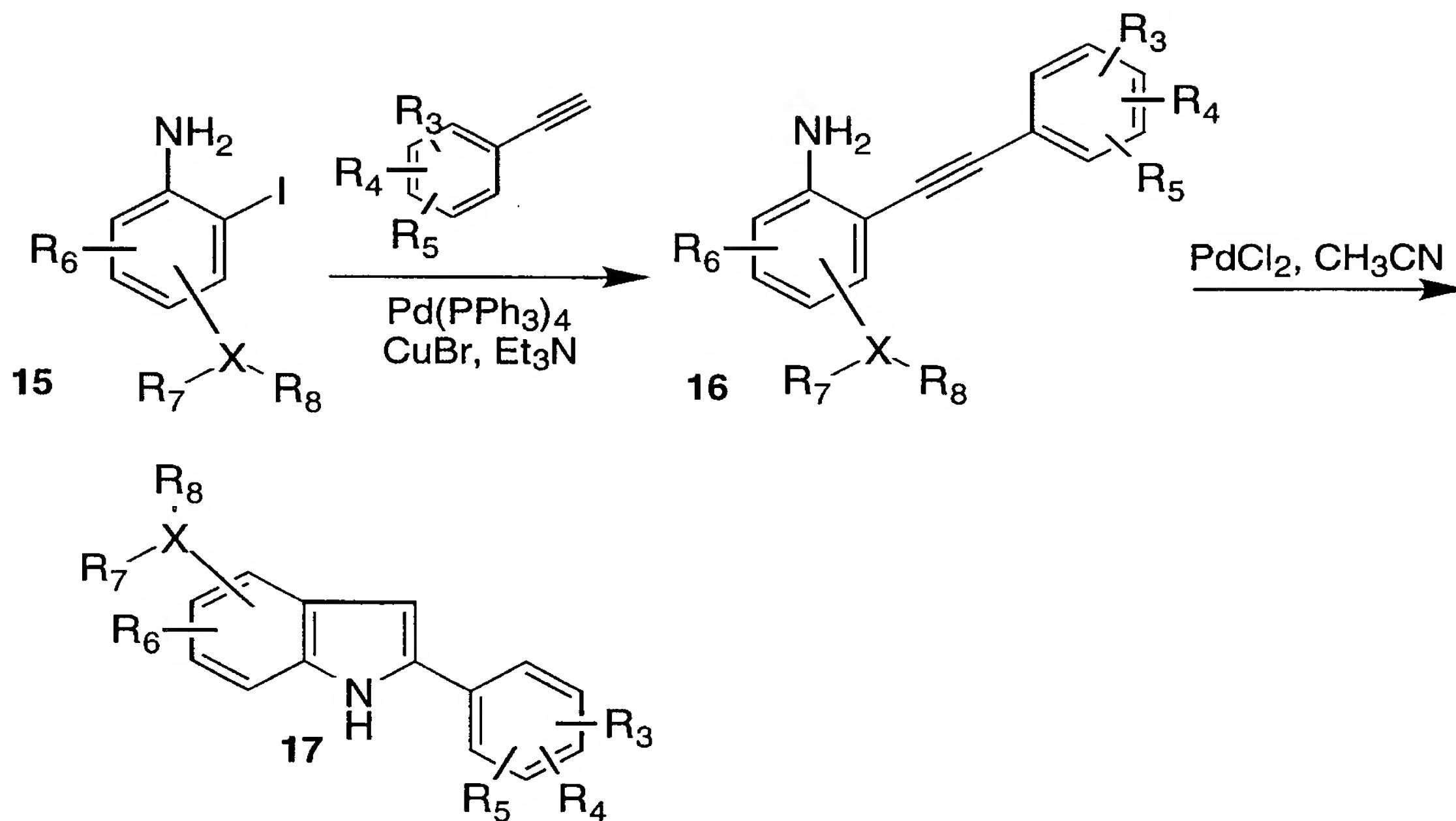
Reaction Scheme E

10 As shown in reaction Scheme E, treatment of an arylhydrazine or arylhydrazine hydrochloride (12) with an arylcyclopropylketone of type (13) in a polar organic solvent such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, preferably n-butanol, at a temperature of 70°-120°C for a period of 8-24 hours gives 2-aryltryptamine (5). Alternatively, when an arylhydrazine or arylhydrazine hydrochloride (12) is treated with an arylbutyl ketone of type (14) containing a leaving group (chloride, bromide, iodide, O-methansulfonate, O-trifluoromethansulfonate, or the like) at the 4-position in a polar solvent such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, or mixtures thereof at room temperature for a period of 30 minutes to 2 hours followed by heating to a temperature of 65°-100°C for 4-24 hours, 2-aryltryptamine (5) is produced.

15

20

Scheme F

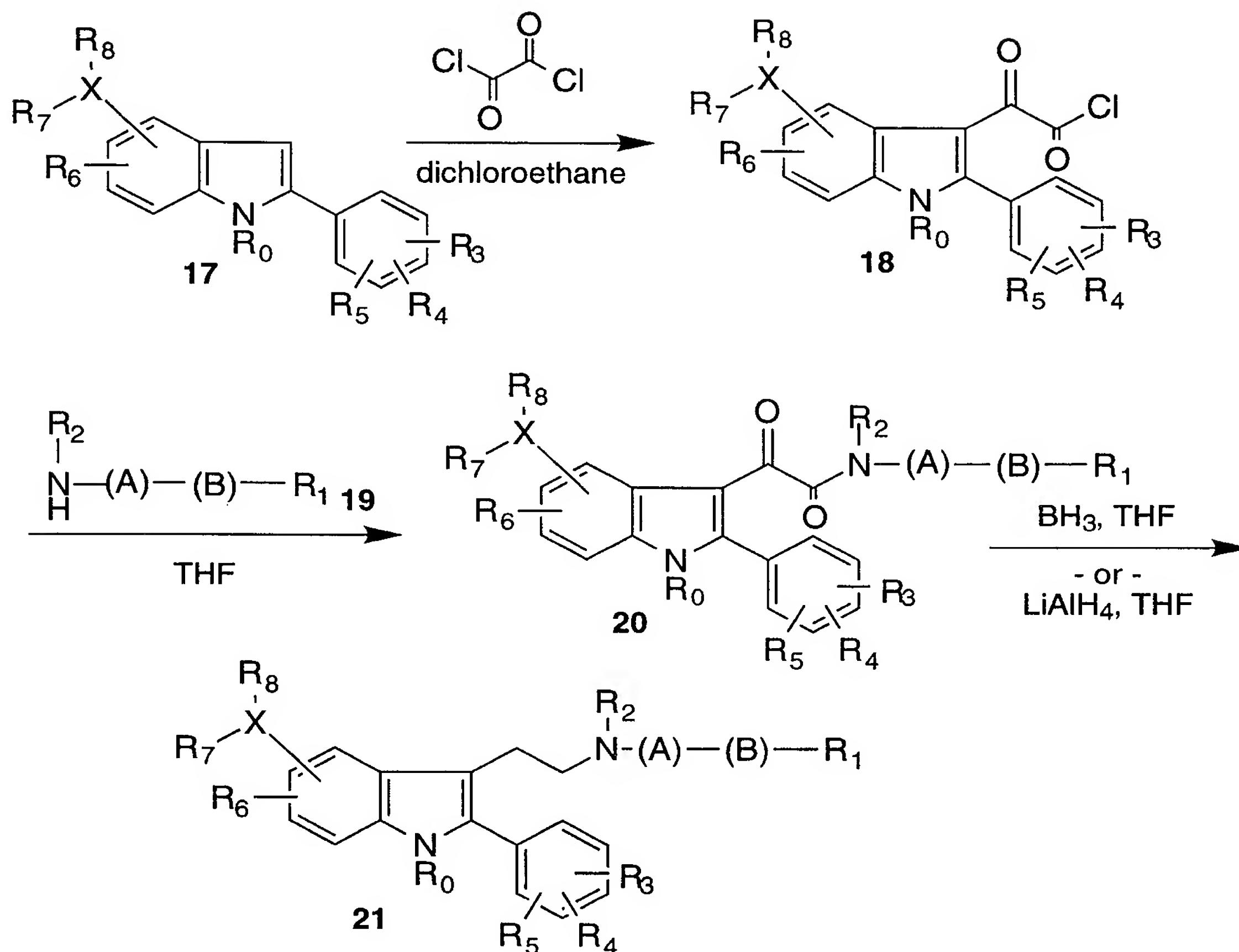


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Reaction Scheme F

As shown in reaction Scheme F, iodoanilines of type (15) may be reacted with aryl acetylenes, an appropriate palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium, a copper (I) halide such as cuprous bromide in an inert organic solvent such as triethylamine at a temperature of 50°-88°C for a period of 30 minutes to 5 hours to provide the diarylacetylene (16). Acetylene (16) may be further modified by treatment with a palladium (II) catalyst such as palladium (II) chloride or palladium (II) acetate in an inert organic solvent such as acetonitrile at a temperature of 50°- 82°C for a period of 30 minutes to 6 hours to give 2-arylindole (17).

Scheme G



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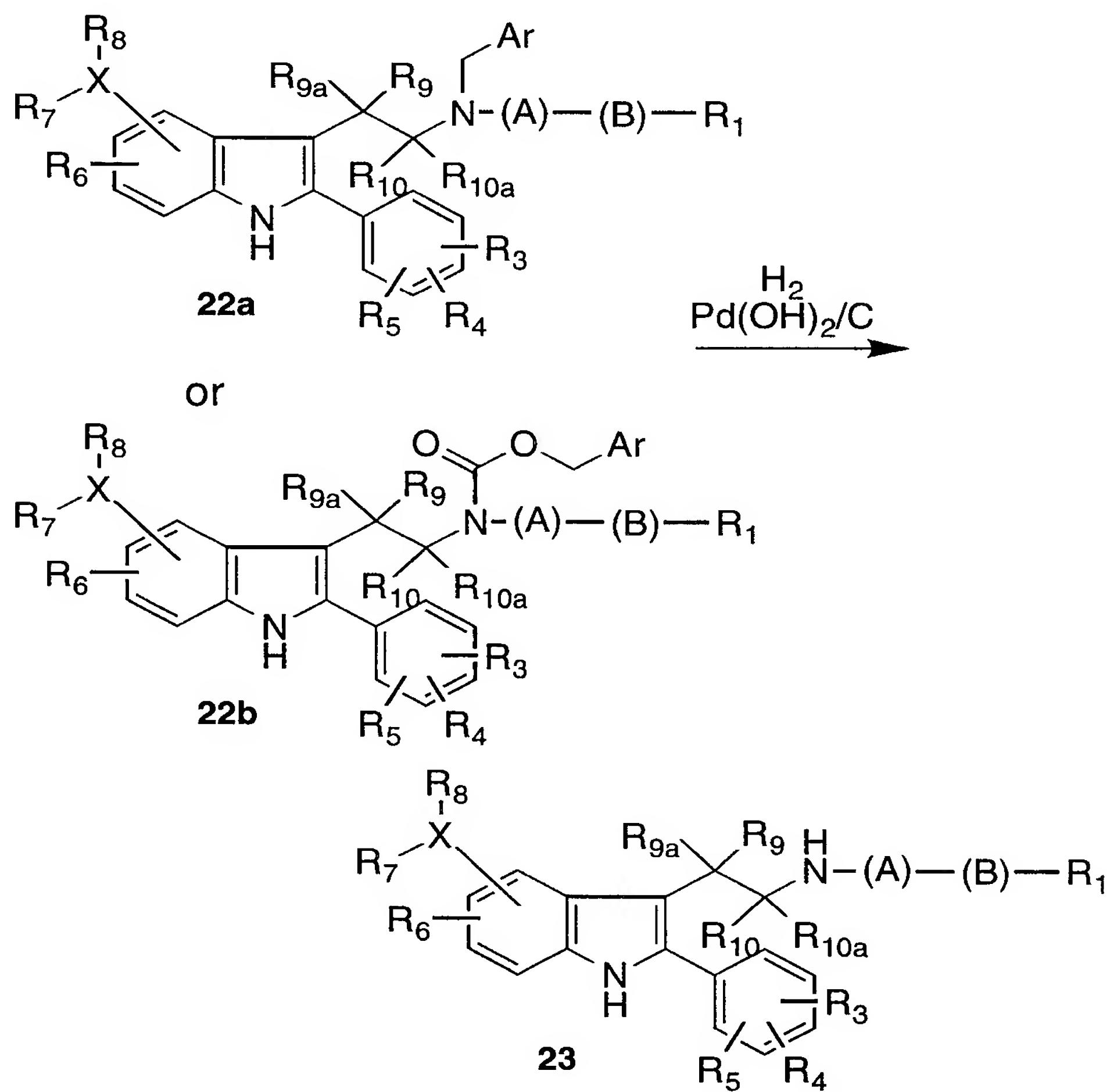
Reaction Scheme G

As shown in reaction Scheme G, treatment of 2-arylidindole (17) with oxalyl chloride neat or in an inert organic solvent such as methylene chloride, chloroform, dichloroethane, tetrahydrofuran or the like at a temperature of 25°-65°C for a period of 3-24 hours gives the acylchloride adduct (18). The crude product (18) may be reacted with an amine of type (19) in an inert organic solvent such as diethylether, tetrahydrofuran, methylene chloride, chloroform or the like and an amine base such as triethylamine, diisopropylethylamine or pyridine at a temperature of 0°C-25°C for a period of 30 minutes to 4 hours to provide the amide derivative (20). Amide (20) may be further modified by treatment with a reducing agent such as borane or lithium aluminum

hydride in an inert organic solvent such as tetrahydrofuran at elevated temperatures, preferably reflux, for a period of 1-5 hours to give compound (21).

5

Scheme H



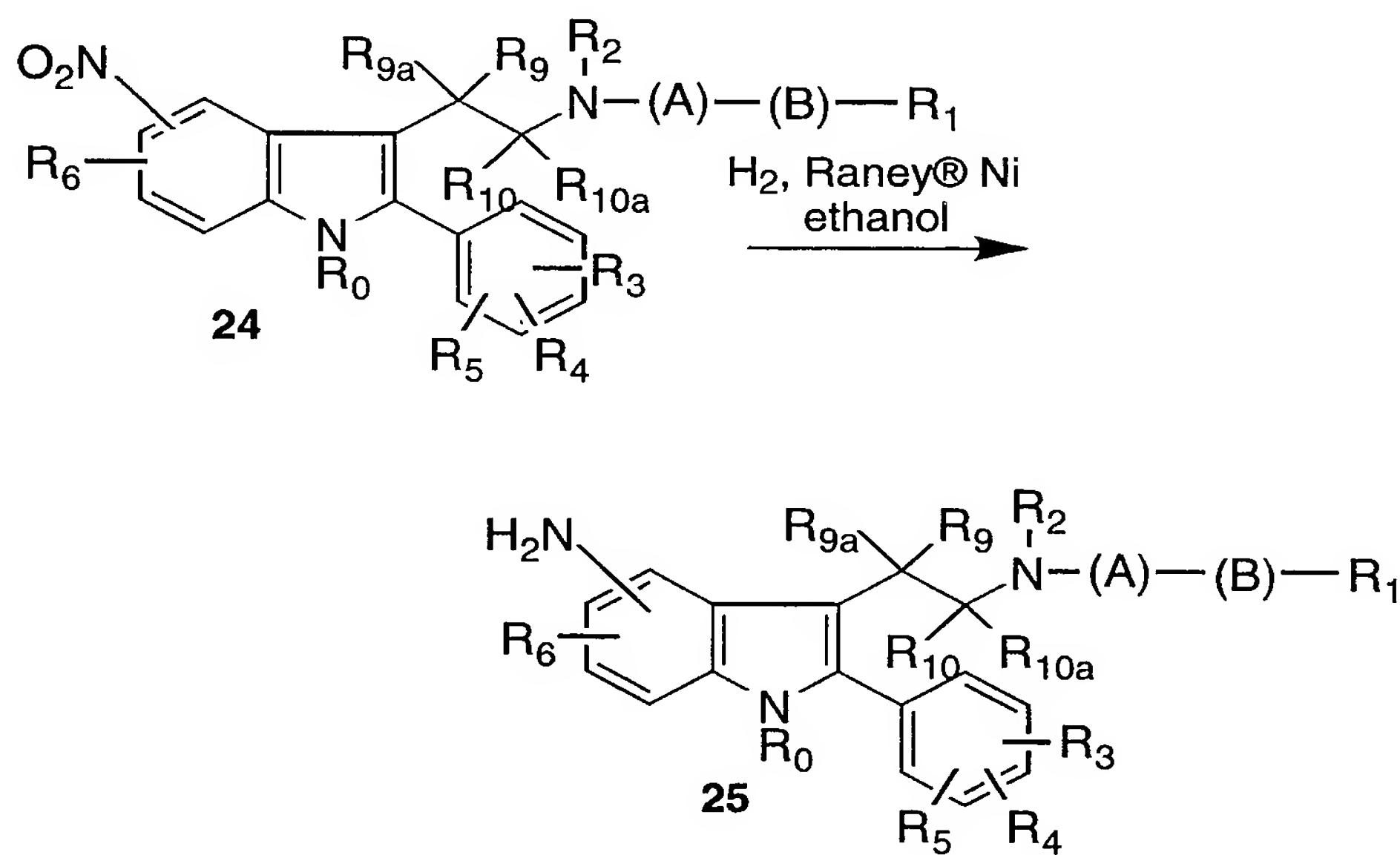
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Reaction Scheme H

As shown in reaction Scheme H, N-benzyl derivatives of type (22a) or N-benzyloxycarbonyl derivatives of type (22b) may be reduced to provide the secondary amine analogs (7) by treatment with hydrogen (1 atm) and an appropriate catalyst such as palladium on carbon,

palladium hydroxide on carbon, or the like in an inert organic solvent such as tetrahydrofuran, ethyl acetate, methanol, ethanol, or mixtures thereof to which has been added a weak acid such as 30% aqueous acetic acid for a period of 10 minutes to 3 hours or until the aryl group has been
5 removed to give the secondary amine.

Scheme I

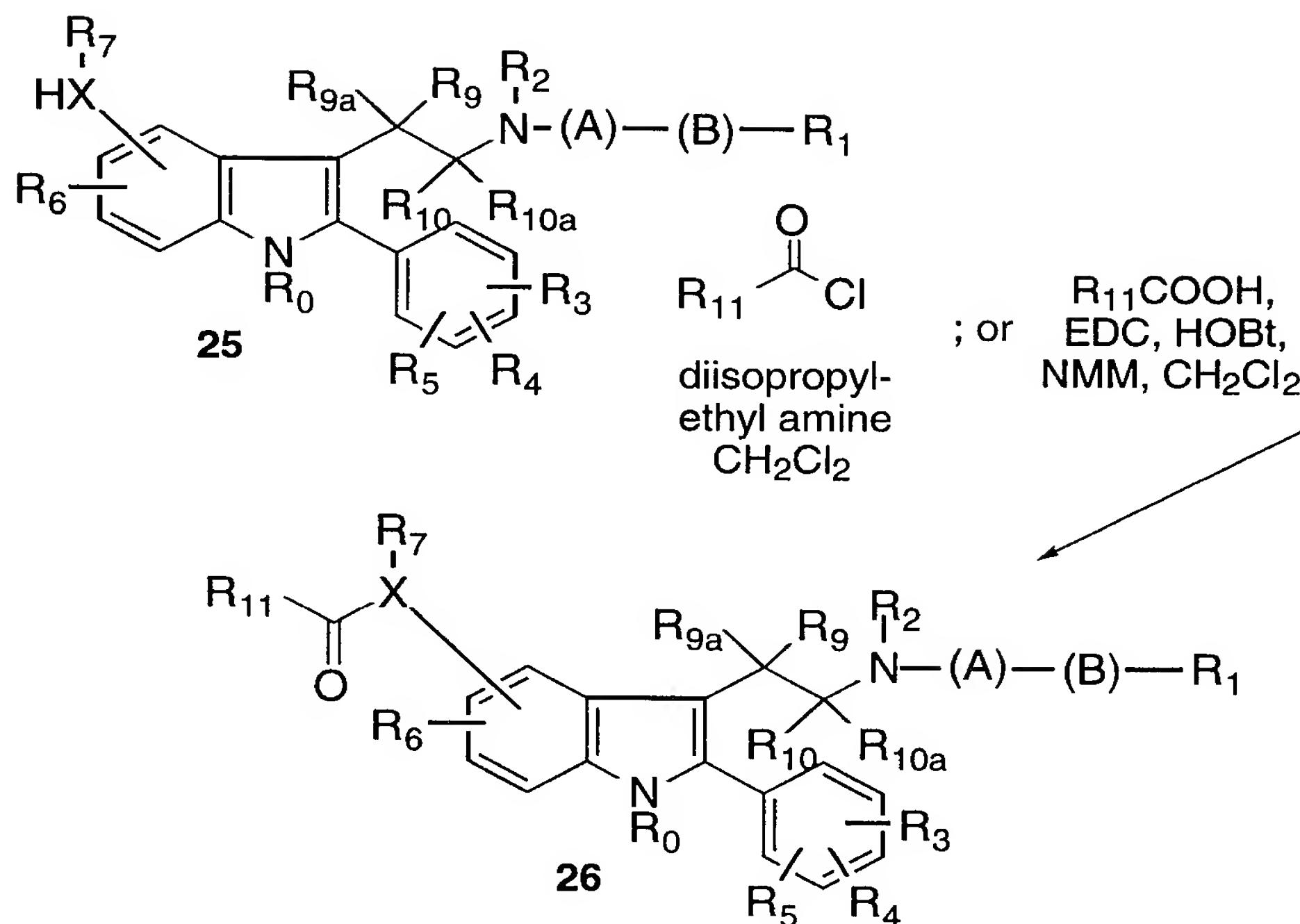


10

Reaction Scheme I

As shown in reaction Scheme I, treatment of a nitroindole of type (24) with hydrogen (1 atm) and an appropriate catalyst such as
15 Raney® Nickel in an inert organic solvent such as ethanol, methanol, or the like at room temperature for a period of 2-12 hours gives the corresponding aminoindole derivative (25).

Scheme J



5

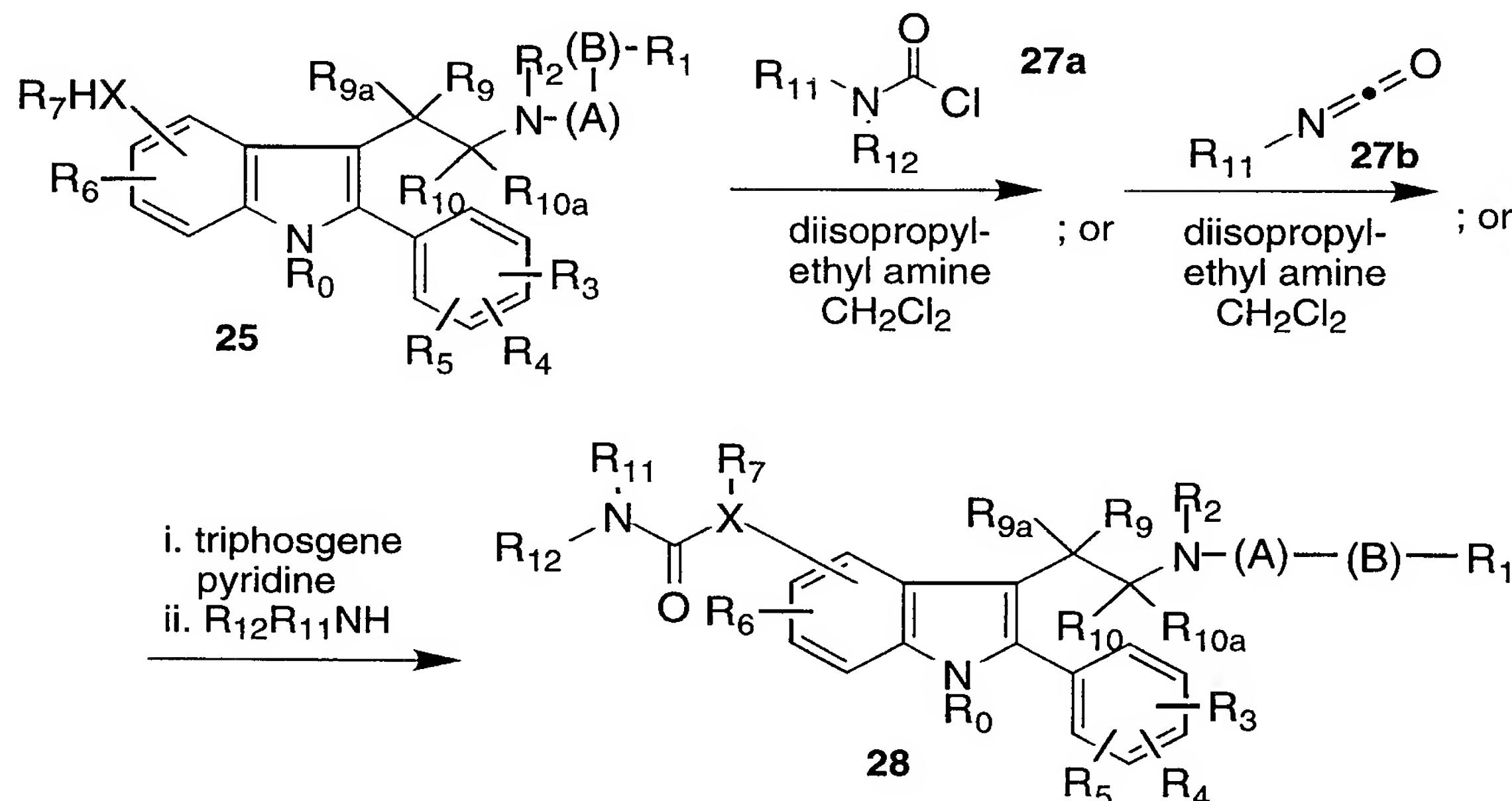
Reaction Scheme J

As shown in reaction Scheme J, amino- or hydroxyindole (25) may be modified by acylation under a variety of conditions. For example, treatment of (25) with an acid chloride, acid anhydride or active ester and an amine base such as triethylamine, diisopropylethylamine, pyridine, or the like in an inert organic solvent such as methylene chloride, chloroform, tetrahydrofuran, or mixtures thereof at 0°C to room temperature for a period of 1 to 12 hours gives the corresponding amide or ester derivatives (26). Alternatively (25) may be coupled with a carboxylic acid by one of the many dehydrating agents commonly employed. For instance, treatment of aminoindole (25) with an appropriate carboxylic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or the like with or without 1-hydroxybenzotriazole (HOBT) and a tertiary amine base such as N-methylmorpholine (NMM), triethylamine or the like in an inert organic solvent such as methylene chloride,

chloroform, dimethylformamide, or mixtures thereof at or near room temperature for a period of 3-24 hours provides the corresponding amide or ester derivative (26).

5

Scheme K



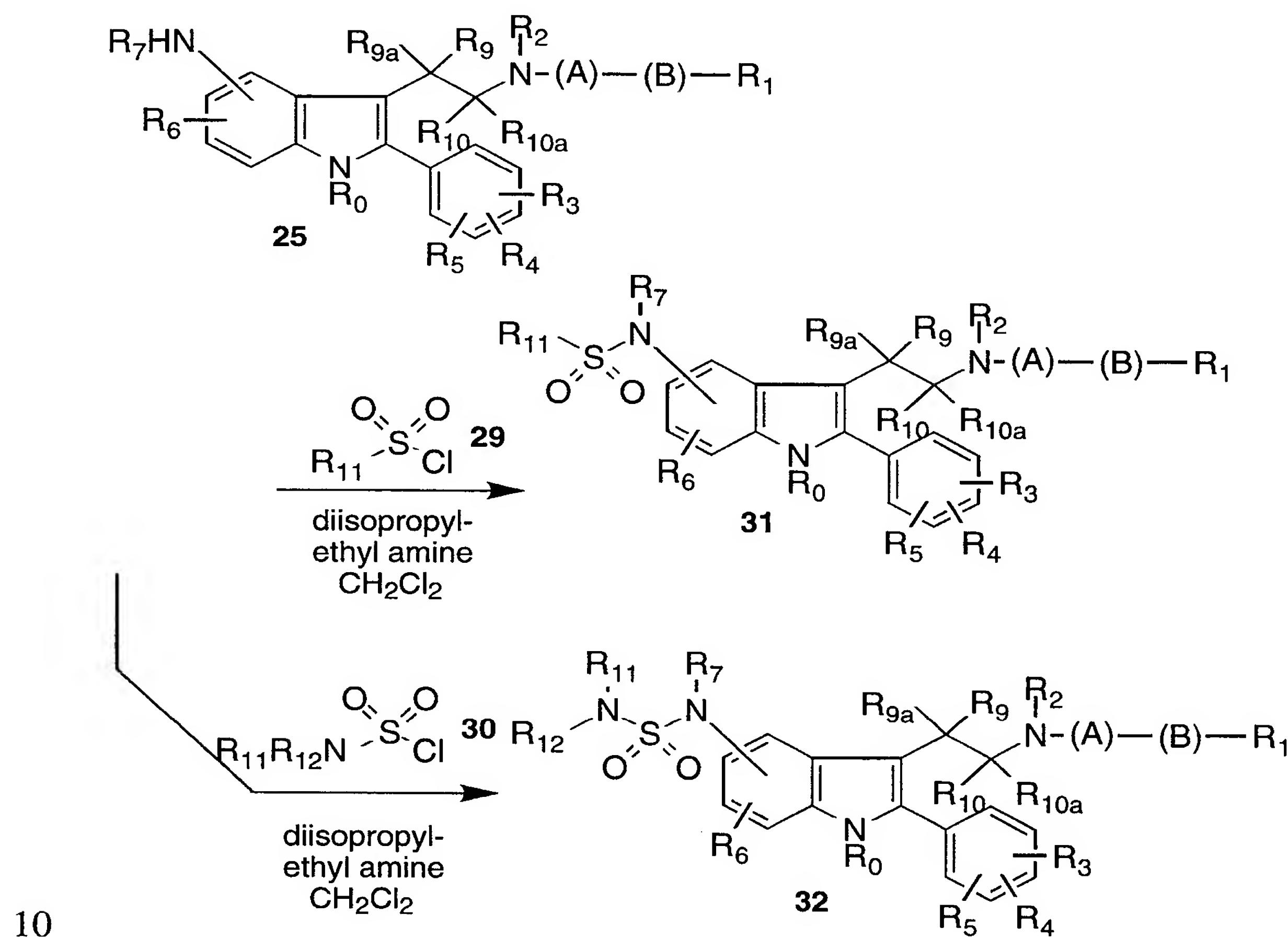
Reaction Scheme K

10

As shown in reaction Scheme K, urea or carbamate derivatives of (25) can be prepared by treatment with a carbamoyl chloride of type (27a), or alternatively with an isocyanate reagent of type (27b), and an amine base such as pyridine, triethylamine, diisopropylethylamine, *N*-methylmorpholine or the like in an inert organic solvent such as methylene chloride, chloroform, dimethylformamide, tetrahydrofuran or mixtures thereof at a temperature of 0°-65°C for a period of 1-72 hours to give (28). Compound (25) can also be modified by treatment with a bis(electrophilic) reagent such as phosgene, triphosgene, 1,1'-carbonyldiimidazole, *N,N'*-disuccinimidyl carbonate, or the like with or without the addition of an amine base such as pyridine, triethylamine, diisopropylethylamine,

5 *N*-methylmorpholine in an inert solvent such as methylene chloride, chloroform, or the like at a temperature of -20°-0°C for a period of 20 minutes to 2 hours. After this time, the reaction mixture is treated with an appropriate mono- or disubstituted amine at -20° to 25°C for a period of 1-5 hours to give the urea or carbamate analog (28).

Scheme L



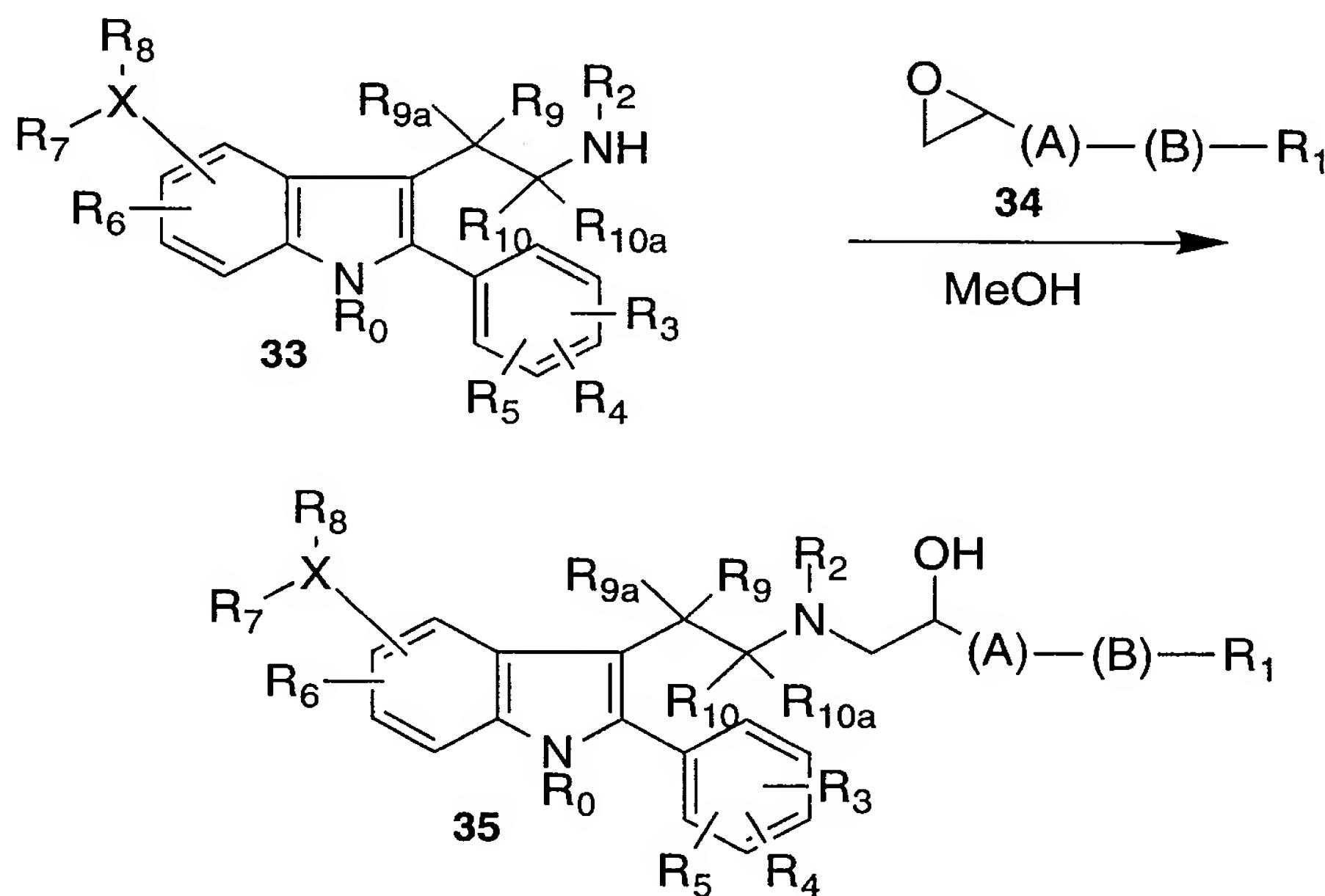
Reaction Scheme L

As shown in reaction Scheme L, amine (25) can be modified by treatment with an appropriate sulfonyl chloride of type (29) or sulfamyl chloride of type (30) with an amine base such as pyridine, triethylamine, diisopropylethylamine, *N*-methylmorpholine in an inert

solvent such as methylene chloride, chloroform, dichloroethane or the like at a temperature of -20°-25°C for a period of 20 minutes to 2 hours to give the corresponding *N*-sulfonamide (31) or *N*-sulfamylamide (32) derivatives, respectively.

5

Scheme M

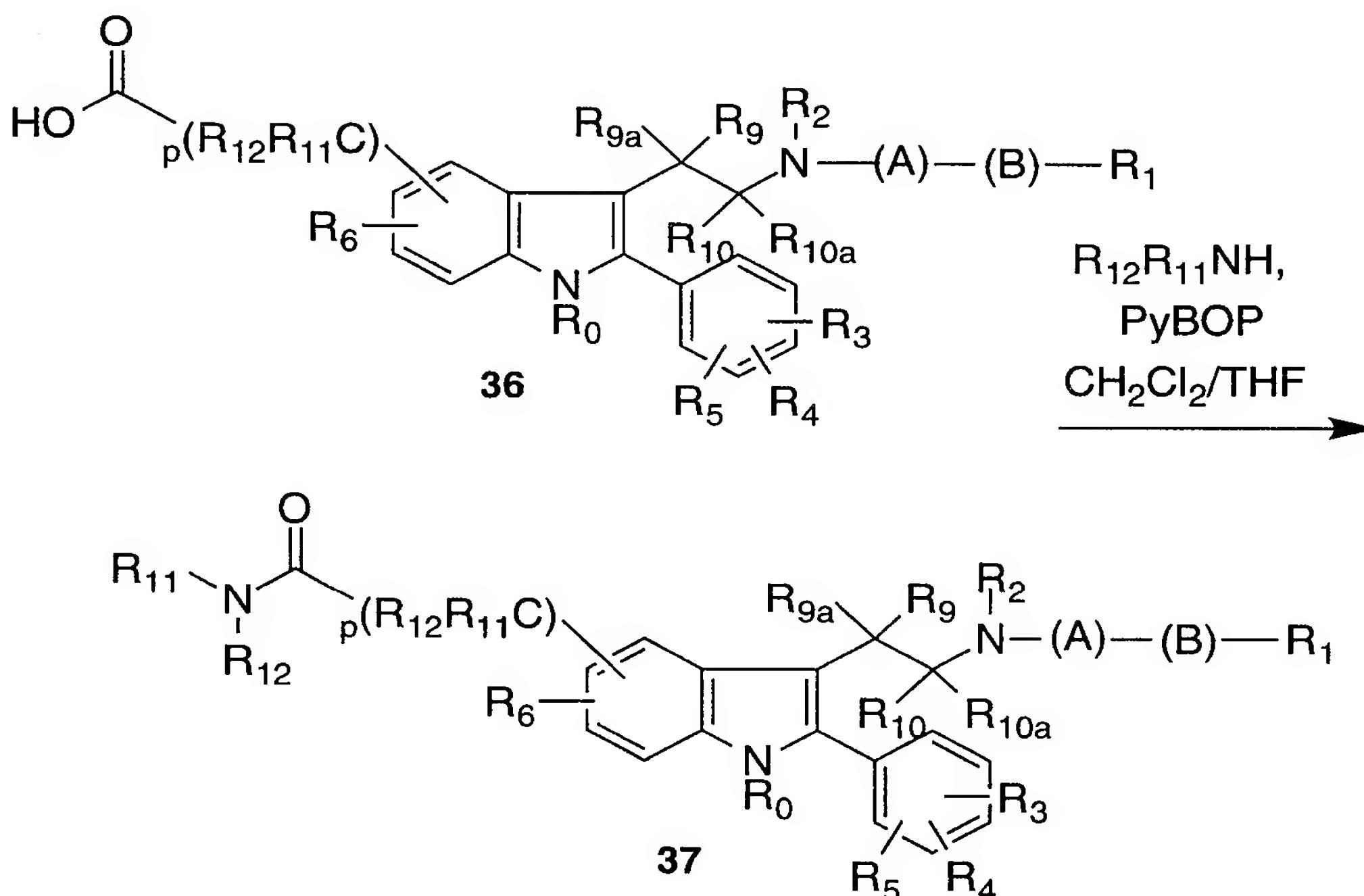


10

Reaction Scheme M

As shown in reaction Scheme M, the 2-aryltryptamine (33) can be modified by treatment with an epoxide such as (34) in an inert organic solvent such as methanol, ethanol, isopropanol, butanol, tert-butanol, or mixtures thereof at a temperature of 65°-110°C for a period of 8-20 hours to give the corresponding amino-alcohol derivative (35).

Scheme N

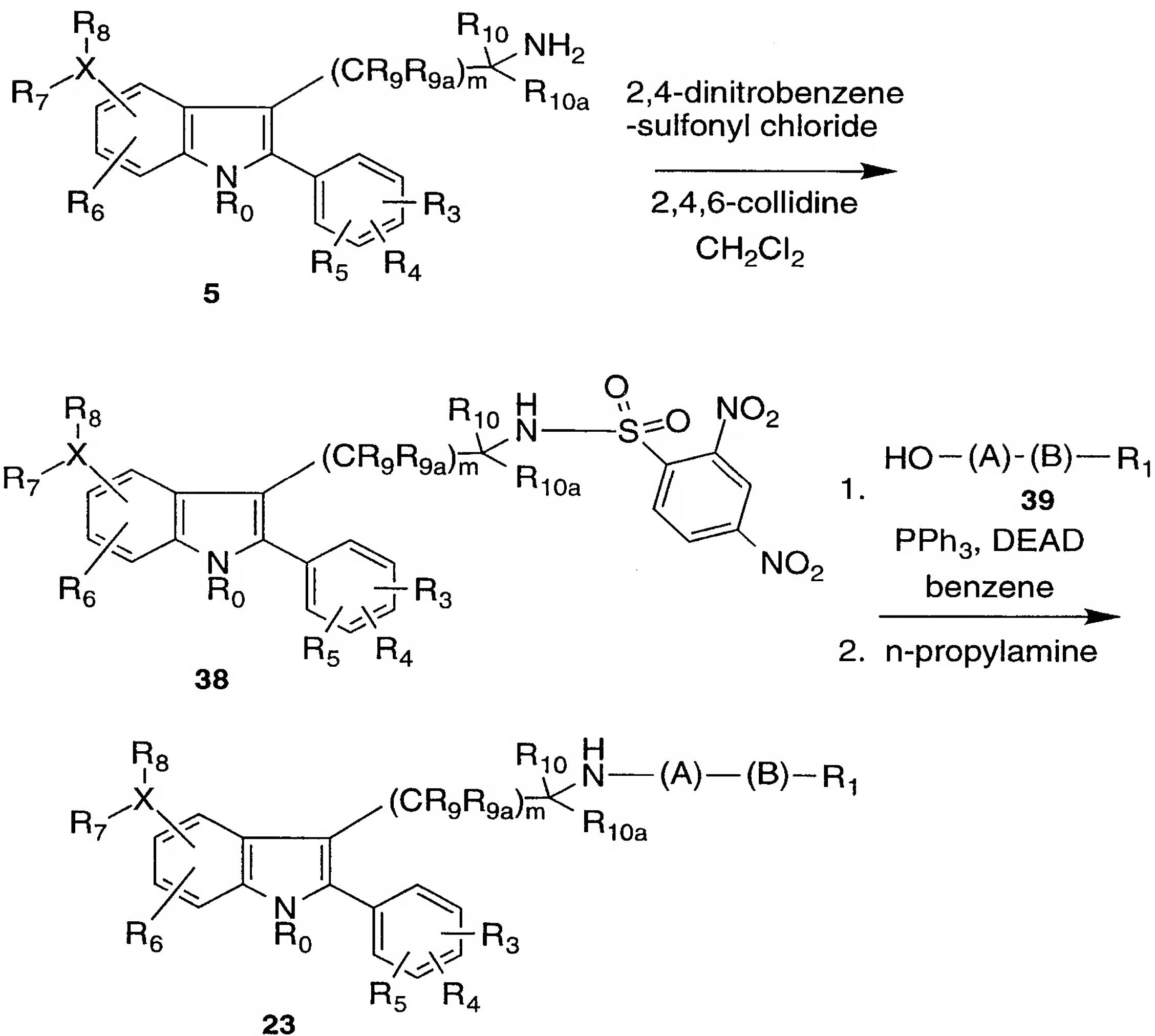


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Reaction Scheme N

As shown in reaction Scheme N, amide derivatives of an acid-containing indole derivative such as (36) can be prepared by treatment with an appropriate amine ($\text{R}_{12}\text{R}_{11}\text{ NH}$) and a suitable coupling agent such as benzotriazol-1-yloxy-tris(pyrrolidino) phosphonium hexafluorophosphate (PyBOP), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexylcarbodiimide (DCC) or the like with or without 1-hydroxybenzotriazole (HOBt) and a tertiary amine base such as N-methylmorpholine (NMM), triethylamine or the like in an inert organic solvent such as methylene chloride, chloroform, tetrahydrofuran, dimethylformamide, or mixtures thereof at or near room temperature for a period of 3 hours to 7 days provides the corresponding amide derivative (37).

Scheme O



5

Reaction Scheme O

As shown in reaction Scheme O, the tryptamine 5 can be modified by reaction with an arylsulfonyl chloride such as 10 2-nitrobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride or 2,4-dinitrobenzenesulfonyl chloride and a hindered amine base such as 2,4,6-collidine, 2,6-lutidine or the like in an inert organic solvent such as methylene chloride to provide the corresponding sulfonamide 38. Sulfonamides such as 38 can be further modified by reaction with an 15 alcohol of type 39 in the presence of triphenylphosphine and an

activating agent such as diethyl azodicarboxylate (DEAD), diisopropyl azodicaboylate or the like in an inert organic solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the dialkylsulfonamide adduct. Removal of the sulfonyl group is accomplished by
5 treatment with a nucleophilic amine such as n-propylamine or the like in an inert organic solvent such as methylene chloride to give secondary amines of type **23**.

10 The compounds of the present invention are useful in the treatment of various sex-hormone related conditions in men and women. This utility is manifested in their ability to act as antagonists of the neuropeptide hormone GnRH as demonstrated by activity in the following *in vitro* assays.

15 Human GnRH receptor binding assay

Crude membranes prepared from CHO cells expressing human GnRH receptors were the sources for GnRH receptor. [¹²⁵I]Buserelin (a peptidyl GnRH analog) was used as the radiolabelled ligand. The binding activity was determined as an IC₅₀ which is the antagonist 20 concentration required to inhibit the specific binding of [¹²⁵I]buserelin to GnRH receptors by 50%.

Rat pituitary GnRH receptor binding assay:

Crude plasma membranes prepared from rat pituitary tissues were 25 incubated in a Tris.HCl buffer (50 mM, PH. 7.5) containing bovine serum albumin (.1%), [¹²⁵I]D-t-Bu-Ser₆-Pro₉-ethyl amide-GnRH, and the desired concentration of a test compound. The assay mixtures were incubated at 4°C for 90-120 minutes followed by rapid filtration and repeated washings through a glass fiber filter. The radioactivity of 30 membrane bound radioligands was determined in a gamma-counter. From this data, the IC₅₀ of the radioligand binding to GnRH receptors in the presence of test compound was estimated.

Inhibition of LH release assay:

Active compounds from the GnRH receptor binding assay were further evaluated with an *in vitro* LH release assay to confirm their antagonist 5 activity (blocking GnRH-induced LH release).

1. Sample Preparation

The compounds to be assayed were dissolved and diluted in DMSO. The final concentration of DMSO in the incubation medium was 0.5%.

10

2. Assay

The Wistar male rats (150-200 grams) were obtained from Charles River Laboratories (Wilmington, MA). Rats were maintained at a constant temperature (25°C) on a 12-hr light, 12-hr dark cycle. Rat chow and

15 water were available *ad libitum*. The animals were sacrificed by decapitation and pituitary glands were aseptically removed and placed in Hank's Balanced Salt Solution (HBSS) in a 50-mL polypropylene centrifuge tube. The collection tube was centrifuged for 5 min at 250 x g, and HBSS was removed by aspiration. Pituitary glands were transferred

20 to a disposable petri plate and minced with a scalpel. The minced tissue was then transferred to a 50-mL disposable centrifuge tube by suspending the tissue fragments in three successive 10-mL aliquots of

HBSS containing 0.2% collagenase and 0.2% hyaluronidase. The cell dispersion was carried out in a water bath at 37°C with gentle stirring

25 for 30 min. At the end of the incubation, the cells were aspirated 20 to 30 times with a pipet and the undigested pituitary fragments were allowed to settle for 3 to 5 min. The suspended cells were removed by aspiration, and then subjected to a 1200 x g centrifugation for 5 min. The cells were then resuspended in Culture medium. The undigested pituitary

30 fragments were treated with 30 mL aliquots of the digestion enzymes as above for a total of 3 digestions with the collagenase/hyaluronidase mixture. The resulting cell suspensions were pooled, counted and diluted to a concentration of 3×10^5 cells/ml, and 1.0 ml of this

35 suspension was placed in each well of a 24-well tray (Costar, Cambridge, MA). Cells were maintained in a humidified 5% CO₂-95% air

atmosphere at 37°C for 3 to 4 days. The culture medium consisted of DMEM containing 0.37% NaHCO₃, 10% horse serum, 2.5% fetal bovine serum, 1% non-essential amino acids, 1% glutamine, and 0.1% gentamycin. On the day of an experiment, cells were washed three 5 times 1 1/2 hrs prior to and two more times immediately before the start of the experiment with DMEM containing 0.37% NaHCO₃, 10% horse serum, 2.5% fetal bovine serum, 1% non-essential amino acids(100X), 1% glutamine(100X), 1% Penicillin/Streptomycin(10,000 Units of Penicillin and 10,000 micrograms of Streptomycin per ml), and 25 mM 10 HEPES, pH 7.4. LH release was initiated by adding 1 ml of fresh medium containing test compounds in the presence of 2 nM GnRH to each well in duplicate. Incubation was carried out at 37°C for 3 hr. After incubation, medium was removed and centrifuged at 2,000 x g for 15 min to remove any cellular material. The supernatant fluid was 15 removed and assayed for LH content with a double antibody RIA procedure using materials obtained from Dr. A. F. Parlow (Harbor-UCLA Medical Center, Torrance, CA).

The compounds of formula I are useful in a number of areas affected by GnRH. They may be useful in sex-hormone related 20 conditions, sex-hormone dependent cancers, benign prostatic hypertrophy or myoma of the uterus. Sex-hormone dependent cancers which may benefit from the administration of the compounds of this invention include prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrope adenomas. Other sex-hormone dependent 25 conditions which may benefit from the administration of the compounds of this invention include endometriosis, polycystic ovarian disease, uterine fibroids and precocious puberty. The compounds may also be used in combination with an angiotensin-converting enzyme inhibitor such as Enalapril or Captopril, an angiotensin II-receptor antagonist 30 such as Losartan or a renin inhibitor for the treatment of uterine fibroids.

The compounds of the invention may also be useful for controlling pregnancy, as a contraceptive in both men and women, for 35 *in vitro* fertilization, in the treatment of premenstrual syndrome, in the treatment of lupus erythematosis, in the treatment of hirsutism, in the

treatment of irritable bowel syndrome and for the treatment of sleep disorders such as sleep apnea.

A further use of the compounds of this invention is as an adjunct to growth hormone therapy in growth hormone deficient children. The compounds may be administered with growth hormone or a compound which increases the endogenous production or release of growth hormone. Certain compounds have been developed which stimulate the release of endogenous growth hormone. Peptides which are known to stimulate the release of endogenous growth hormone include growth hormone releasing hormone, the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890, PCT Patent Pub. No. WO 89/07110, and PCT Patent Pub. No. WO 89/07111) and GHRP-2 (described in PCT Patent Pub. No. WO 93/04081), as well as hexarelin (J. Endocrinol Invest., 15(Suppl 4), 45 (1992)). Other compounds which stimulate the release of endogenous growth hormone are disclosed, for example, in the following: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

Representative preferred growth hormone secretagogues employed in the present combination include the following:

- 1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 5 2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 10 3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 15 4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 20 5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide;
- 25 6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;
- 7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate;
- 30 8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;
- 9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide;

5 12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide;

10 13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide;

15 14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

20 15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

25 16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

30 17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

The compounds of the invention may also be used in combination with bisphosphonates (bisphosphonic acids) and other agents, such as growth hormone secretagogues, e.g. MK-0677, for the

treatment and the prevention of disturbances of calcium, phosphate and bone metabolism, in particular, for the prevention of bone loss during therapy with the GnRH antagonist, and in combination with estrogens, progesterones and or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with the GnRH antagonist.

Bisphosphonates (bisphosphonic acids) are known to inhibit bone resorption and are useful for the treatment of bone lithiasis as disclosed in U.S. Patent 4,621,077 to Rosini, et al.

The literature discloses a variety of bisphosphonic acids which are useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Patent No. 3,251,907; U.S. Patent No. 3,422,137; U.S. Patent No. 3,584,125; U.S. Patent No. 3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,578,376; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,761,406; U.S. Patent No. 4,922,007; U.S. Patent No. 4,942,157; U.S. Patent No. 5,227,506; U.S. Patent No. 5,270,365; EPO Patent Pub. No. 0,252,504; and J. Org. Chem., 36, 3843 (1971).

The preparation of bisphosphonic acids and halo-bisphosphonic acids is well known in the art. Representative examples may be found in the above mentioned references which disclose the compounds as being useful for the treatment of disturbances of calcium or phosphate metabolism, in particular, as inhibitors of bone resorption.

Preferred bisphosphonates are selected from the group of the following compounds: alendronic acid, etidrononic acid, clodronic acid, pamidronic acid, tiludronic acid, risedronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid, and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid; or any pharmaceutically acceptable salt thereof. A particularly preferred bisphosphonate is alendronic acid (alendronate), or a pharmaceutically acceptable salt thereof. An especially preferred bisphosphonate is alendronate sodium, including alendronate sodium

trihydrate. Alendronate sodium has received regulatory approval for marketing in the United States under the trademark FOSAMAX®.

Additionally, a compound of the present invention may be co-administered with a 5a-reductase 2 inhibitor, such as finasteride or 5 epristeride; a 5a-reductase 1 inhibitor such as 4,7b-dimethyl-4-aza-5a-cholestan-3-one, 3-oxo-4-aza-4,7b-dimethyl-16b-(4-chlorophenoxy)-5a-androstane, and 3-oxo-4-aza-4,7b-dimethyl-16b-(phenoxy)-5a-androstane as disclosed in WO 93/23420 and WO 95/11254; dual inhibitors of 5a-reductase 1 and 5a-reductase 2 such as 3-oxo-4-aza-17b-(2,5-10 trifluoromethylphenyl-carbamoyl)-5a-androstane as disclosed in WO 95/07927; antiandrogens such as flutamide, casodex and cyproterone acetate, and alpha-1 blockers such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin.

Further, a compound of the present invention may be used 15 in combination with growth hormone, growth hormone releasing hormone or growth hormone secretagogues, to delay puberty in growth hormone deficient children, which will allow them to continue to gain height before fusion of the epiphyses and cessation of growth at puberty.

For combination treatment with more than one active 20 agent, where the active agents are in separate dosage formulations, the active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agent.

The pharmaceutical compositions containing the active 25 ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical 30 compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically 35 acceptable excipients which are suitable for the manufacture of tablets.

These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or 5 acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glycetyl 10 monostearate or glycetyl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert 15 solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in 20 admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring 25 phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or 30 condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one

or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been

mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water,

5 Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

10 Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release 15 the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

20 The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage 25 administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of 30 polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of 35 administration; the renal and hepatic function of the patient; and the

particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving 5 concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of structural formula I useful in the method 10 of the present invention range from 0.01 to 1000 mg per adult human per day. Most preferably, dosages range from 0.1 to 500 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active 15 ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of 20 body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in dividend doses of two, three or four times daily.

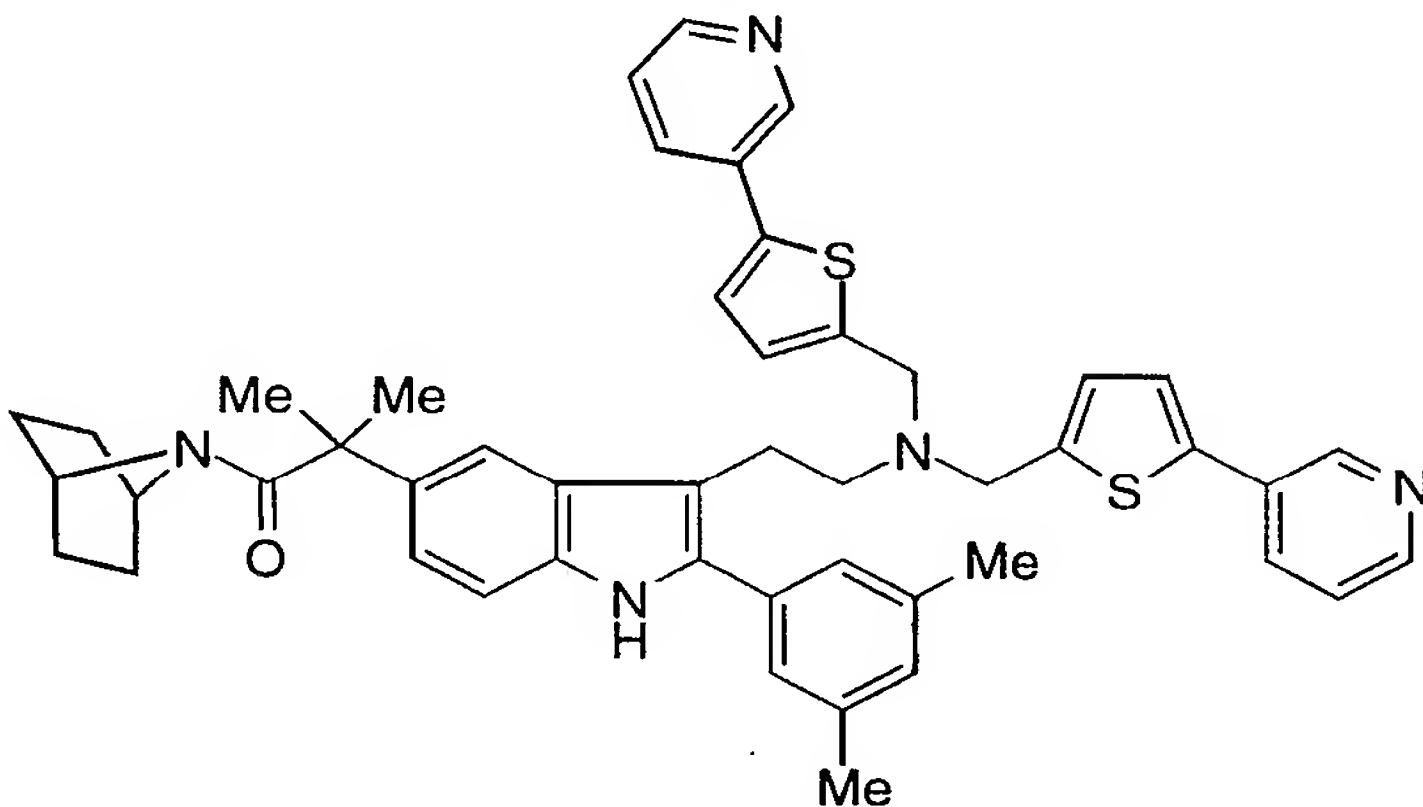
25 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level 30 for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate the preparation of some of the compounds of the invention and are not to be construed as limiting the invention disclosed herein.

5

EXAMPLE 1



1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-[3-[2-[bis-(5-pyridin-3-yl-thiophen-2-ylmethyl)aminolethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropan-1-one

Step 1A 2-[3-(2-Aminoethyl)-2-(3,5-dimethyl-phenyl)-1H-indol-5yl]-2-methylpropionic acid ethyl ester

A mixture of 10.50 g of ethyl 2-(4-hydrazinophenyl)-2-methylpropionate, 10.55 g of 3-chloropropyl 3,5-dimethylphenyl ketone, and 200 mL of absolute ethanol was stirred under nitrogen and heated to reflux. After 12 hours, the mixture was cooled and filtered. The solid on the filter was washed with additional small volumes of ethanol. The filtrate was treated with 4 mL of concentrated sulfuric acid and stirred at reflux under nitrogen for 4 days. The cooled mixture was stirred in an ice bath as a solution of sodium ethoxide (21% w/w in ethanol) was added dropwise until the mixture was basic by pH paper. The mixture was filtered and concentrated *in vacuo* at 30 °C. The residue was partitioned between diethyl ether and water, with some saturated aqueous sodium chloride solution added to assist in separation of the

layers. The aqueous phase was washed with an additional 100 mL of ether. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residual gum was purified by flash chromatography on silica gel (elution with 97:3:0.3 and then 95:5:0.5
5 methylene chloride:methanol:ammonium hydroxide) to give the title compound (3.9g).

Step 1B 2-[3-(2-*tert*-Butoxycarbonylaminoethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropionic acid ethyl ester
10 To a solution of 2-[3-(2-aminoethyl)-2-(3,5-dimethyl-phenyl)-
1*H*-indol-5-yl]-2-methylpropionic acid ethyl ester (763 mg in 7 mL
tetrahydrofuran) at 0 °C was added a solution of 682 mg di-*tert*-butyl
15 dicarbonate in 3 mL tetrahydrofuran followed by a solution of 432 mg
potassium carbonate in 3 mL water and the resulting suspension stirred
vigourously at 0 °C. After 10 minutes, the reaction was concentrated in
vacuo and the residue dissolved in ethyl acetate. The organic portion
was washed with brine then dried over magnesium sulfate and
concentrated *in vacuo*. The residue was purified by flash
20 chromatography on silica gel (hexane:ethyl acetate, 90:10; then 80:20;
then 70:30) to give the title compound (910 mg).

Step 1C 2-[3-(2-*tert*-Butoxycarbonylaminoethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropionic acid
25 A suspension of 2-[3-(2-*tert*-butoxycarbonylaminoethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropionic acid ethyl ester
(910 mg in 30 mL methanol and 9.5 mL of 2N aqueous potassium
hydroxide) was heated to 95 °C on an oil bath. After 8 hours, the mixture
was cooled to room temperature and the volatile organics removed in
30 vacuo. The aqueous portion was washed with ethyl acetate and the
acidified to pH 4 by the addition of 1N hydrochloric acid. This was then
extracted with ethyl acetate and the organic portion dried over
magnesium sulfate. Concentration in vacuo gave the crude title
compound in quantitative yield.

Step 1D {2-[5-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1H-indol-3-yl}ethyl}carbamic acid *tert*-butyl ester
To a suspension of 2-[3-(2-*tert*-butoxycarbonylaminoethyl)-

5 2-(3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropionic acid (856 mg in 8.0 mL methylene chloride) at 0° C was added 310 mg of 1-hydroxybenzotriazole (HOBT) followed by 400 mg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and the mixture stirred at low temperature for 90 minutes. At this time, a solution of 7-aza-bicyclo

10 [2.2.1]heptane hydrochloride (632 mg in a mixture of 2.0 mL methylene chloride and 0.66 mL triethylamine) was added and the mixture warmed to room temperature. The reaction was quenched after 24 hours by dilution with methylene chloride and washing with half-saturated brine. The combined organics were dried over magnesium

15 sulfate and the concentrate purified by flash chromatography on silica gel (hexane:ethyl acetate, 70:30; then 60:40; then 50:50; then 40:60) to give the title compound (736 mg).

Step 1E 2-[3-(2-Aminoethyl)-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-methyl-propan-1-one
To a solution of {2-[5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxo-ethyl]-2-(3,5-dimethylphenyl)-1H-indol-3-yl}ethyl} carbamic acid *tert*-butyl ester (728 mg in 30 mL methylene chloride) at 0°C was added 1.5 mL anisole followed by 10.5 mL trifluoroacetic acid

25 and the mixture stirred at 0 °C. After 2 hours, the mixture was concentrated *in vacuo* and the residual acid quenched by the addition of 10% ammonium hydroxide in methanol. The concentrated was then purified by flash chromatography on silica gel (methylene chloride:10% ammonium hydroxide in methanol, 95:5; then 92:8) to give the title

30 compound (627 mg).

Step 1F 1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-[3-[2-[bis-(5-pyridin-2-yl-thiophen-2-ylmethyl)aminorethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropan-1-one

To a solution of 2-[3-(2-aminoethyl)-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-1-(7-azabicyclo[2.2.1]hept-7-yl)-2-methyl-propan-1-one in a mixture of dry chloroform and methanol at 0°C was added magnesium sulfate followed by 2.5 equivalents of 5-pyridin-3-yl-thiophene-2-carbaldehyde and the mixture stirred at low temperature. After 40 minutes, acetic acid is added followed by a solution of sodium cyanoborohydride in methanol and the mixture allowed to warm to room temperature. After completion, the reaction is quenched by the addition of saturated aqueous sodium bicarbonate, extracted with methylene chloride and the combined organics washed sequentially with water and brine. Purification of the concentrate by preparative tlc on silica gel gives the title compound.

15

PREPARATION OF SYNTHETIC INTERMEDIATES

Ethyl 2-(4-hydrazinophenyl)-2-methylpropionate

Step A: Ethyl (+/-)-2-(4-nitrophenyl)propionate
20 To a solution of 9.76 g (50 mmol) of (+/-)-2-(4-nitrophenyl) propionic acid in 150 mL of absolute ethanol was added 3.0 mL of concentrated sulfuric acid. The resulting solution was stirred at reflux under nitrogen. After 6 hours, the solution was cooled and stirred vigorously as 250 mL of saturated aqueous sodium bicarbonate solution
25 was added gradually (Caution: foaming). The mixture was then partitioned between 750 mL of ethyl acetate and 500 mL of water. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate solution and then with 100 mL of saturated aqueous sodium chloride solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 10.86 g (97%) of an oil; homogeneous by TLC in 9:1 hexane-ethyl acetate. 400 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure.

30

Step B: Ethyl 2-methyl-2-(4-nitrophenyl)propionate

A suspension of 924 (23 mmol) of sodium hydride (60% in oil) in 21 mL of dry *N,N*-dimethylformamide was stirred under nitrogen in an ice bath as a solution of 4.68 g (21 mmol) of ethyl (+/-)-2-(4-nitrophenyl)propionate in 20.5 mL of dry *N,N*-dimethylformamide was 5 added gradually over about 10 minutes. An intense violet color developed during the addition. The mixture was then allowed to warm to room temperature. After about 1 hour, the mixture was again cooled in an ice bath as a solution of 1.44 mL (3.28 g; 23 mmol) of methyl iodide in 5 mL of dry *N,N*-dimethylformamide was added dropwise by syringe over about 10 minutes, while maintaining the internal temperature at 10-15°C. The mixture was allowed to warm to room temperature, and the color changed to brown. After 1 hour, an additional 187 mL (426 mg, 3 mmol) 15 of iodomethane was added. By the next day, the mixture consisted of a suspension of some grayish solid in a golden liquid. It was stirred vigorously and quenched by gradual addition of 10 mL of 5% aqueous potassium bisulfate solution. The mixture was partitioned between 400 mL of diethyl ether and 400 mL of water. The organic layer was washed with an additional 3 x 400 mL of water and then with 50 mL of saturated aqueous sodium chloride solution. The organic phase was then dried 20 over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (elution with 19:1 hexane-ethyl acetate) yielded 4.31 g (87%) of an oil; homogeneous by TLC in 9:1 hexane-ethyl acetate. 400 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure.

25

Step C: Ethyl 2-(4-Aminophenyl)-2-methylpropionate

A mixture of 4.27 g (18 mmol) of ethyl 2-methyl-2-(4-nitrophenyl)propionate, 200 mg of 10% palladium on carbon, and 120 mL of absolute ethanol was shaken with hydrogen (initial hydrogen 30 pressure 47 psig) in a pressure vessel for 2 hours. The catalyst was removed by filtration through Celite under nitrogen, and the filter cake was washed with additional ethanol. Concentration of the filtrate *in vacuo* at up to 50 °C gave 3.74 g (100%) of an oil; homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ¹H NMR (CDCl₃) was consistent with the 35 assigned structure. Mass spectrum (ESI): m/e = 208 (M + H).

Step D: Ethyl 2-(4-hydrazinophenyl)-2-methylpropionate

A solution of 3.725 g (18 mmol) of ethyl 2-(4-aminophenyl)-2-methylpropionate in 18 mL of concentrated hydrochloric acid was stirred 5 at -10 to -5 °C in an ice-acetone bath as a solution of 1.29 g (18.7 mmol) of sodium nitrite in 7.5 mL of water was added dropwise over about 15 minutes. Stirring was continued at this temperature for an additional 10 30 minutes. Next, a small amount of insoluble solid was removed by filtration into a cold receiving flask. The filtrate was then added dropwise over 10-15 minutes to a solution of 20.3 g (90 mmol) of stannous chloride dihydrate in 14.5 mL of concentrated hydrochloric acid stirred under nitrogen in an ice-acetone bath. The addition was carried out at such a rate that the internal temperature remained at about -5 °C. A 15 gummy material separated during the addition. After completion of the addition, stirring was continued at -10 to -5 °C for 1 hour. The aqueous phase was decanted, and the residual gum was dissolved in 250 mL of ethyl acetate. The ethyl acetate solution was treated cautiously with 250 mL of saturated aqueous sodium bicarbonate solution and shaken in a separatory funnel. The ethyl acetate layer was washed with 50 mL of 20 saturated aqueous sodium chloride solution. The entire mixture was filtered before separation of the phases. The ethyl acetate phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* at room temperature to yield 2.59 g (65%) of an oil. 500 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure and indicated that 25 only minor impurities were present.

3-Chloropropyl 3,5-dimethylphenyl ketone30 Step AA: 4-Chloro-N-methoxy-N-methylbutyramide

To a solution of 4-chlorobutyryl chloride (10.0 g in 200 mL of dry methylene chloride) was added 10.4 g of *N,O*-dimethylhydroxylamine hydrochloride. The mixture was stirred under nitrogen and maintained below 25 °C by cooling in an ice bath as necessary while triethylamine 35 (29.1 mL) was added dropwise over about 20 minutes, resulting in

precipitation. After 1.5 hours at room temperature, the mixture was concentrated *in vacuo*. The residue was partitioned between 100 mL of diethyl ether and 100 mL of saturated aqueous sodium bicarbonate solution. The organic layer was washed with an additional 100 mL of 5 saturated sodium bicarbonate, and the aqueous fractions were back-extracted with ether. The combined organic phases were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 10.5 g (90%) of an oil, which had satisfactory purity by ^1H NMR (CDCl_3). Mass spectrum (PB-NH₃/CI): m/e = 166 (M + H).

10

Step BB: 3-Chloropropyl 3,5-dimethylphenyl ketone

A solution of 10.2 mL (13.9 g; 72 mmol) 5-bromo-*m*-xylene in 200 mL of anhydrous tetrahydrofuran was stirred under nitrogen at -78°C as 35.8 mL (84 mmol) of 2.5 M *n*-butyllithium in tetrahydrofuran was added dropwise. After 15 minutes at -78°C, a solution of 10.0 g (60 mmol) of 4-chloro-*N*-methoxy-*N*-methylbutyramide in 30 mL of anhydrous tetrahydrofuran was added dropwise over 25-30 minutes. The resulting solution was maintained at -78°C for 45 minutes and then warmed briefly to room temperature. The reaction was quenched by 20 addition of 40 mL of 2 N hydrochloric acid and then partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous sodium bicarbonate solution and then saturated aqueous sodium chloride solution. The organic solution was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography of 25 the residue afforded 8.91 g (70%) of an oil, which had satisfactory purity by ^1H NMR (CDCl_3).

5-Pyridin-3-yl-thiophene-2-carbaldehyde

30 Step AAA: Pyridine-3-boronic acid

To a solution of *n*-butyllithium (16 mL of a 2.5M solution in hexane = 50 mL dry diethyl ether) at -78° C was added a solution of 3-bromopyridine (6 g in 15 mL diethyl ether) and the mixture stirred for 25 minutes. At this time trimethyl borate (4.3 mL) was added and the

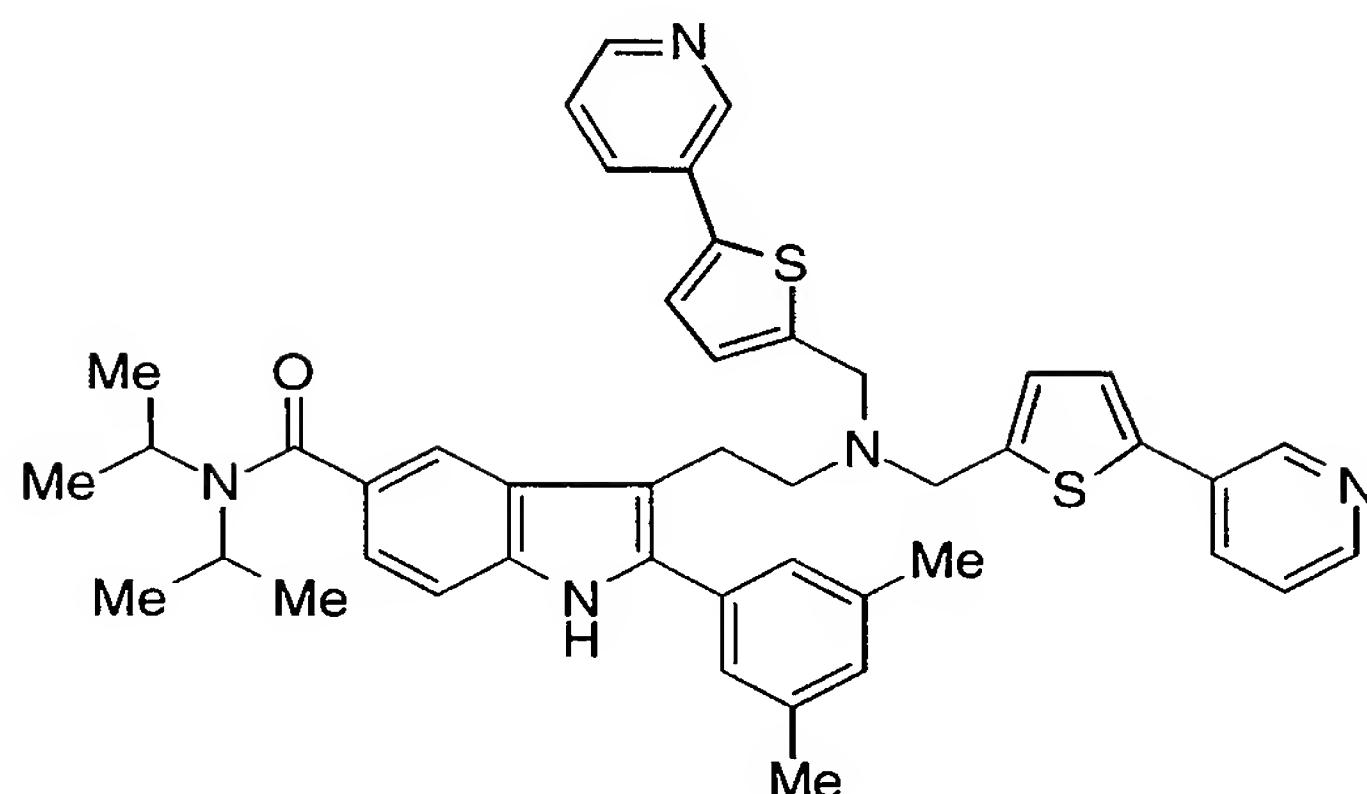
mixture allowed to warm to room temperature. After 1 hour the reaction was quenched by the addition of 10 mL glacial acetic acid and 60 mL water and the mixture stirred for 18 hours at room temperature. The pH of the mixture was adjusted to pH12 by the addition of 2M sodium 5 hydroxide and extracted with diethyl ether. The aqueous layer was acidified to pH 6 by the dropwise addition of 1N hydrochloric acid and extracted with methylene chloride. The combined organics were dried over magnesium sulfate and concentrated *in vacuo*. The residue was triturated with 20 mL acetonitrile:water (1:1) and filtered to give the title 10 compound (1.0 g).

Step BBB: (5-pyridin-3-yl-thiophen-2-yl)-methanol

To a mixture of 153 mg (5-bromo-thiophen-2-yl)-methanol, 128 mg pyridine-3-boronic acid, and 64 mg tetrakis(triphenylphosphine) 15 palladium was added solvent (7.3 mL toluene and 3.1 mL methanol) followed by 1.4 mL of 2.5M sodium carbonate and the mixture heated to 80 °C on an oil bath. After 16 hours the mixture was cooled to room temperature and concentrated *in vacuo*. The residue was solvated in ethyl acetate was washed sequentially with 0.5N sodium hydroxide and 20 brine, dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel (hexane:ethyl acetate, 60:40; then 55:45) gave the title compound (147 mg).

Step CCC: 5-Pyridin-3-yl-thiophene-2-carbaldehyde

25 To a solution of (5-pyridin-3-yl-thiophen-2-yl)-methanol (144 mg in 7.5 mL dry methylene chloride) was added 327 mg of the 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one and the mixture stirred at room temperature. After 4 hours, the reaction was quenched by addition of a mixture of saturated sodium bicarbonate and saturated 30 sodium thiosulfite (1:1) and extracted with diethyl ether. The aqueous portion was extracted further with methylene chloride and the combined organics then washed with water and brine and dried over magnesium sulfate. Purification of the concentrate by flash chromatography on 35 silica gel (ethyl acetate:hexane, 75:25; then 80:20) gave the title compound (80 mg).

EXAMPLE 2

5 3-{2-[Bis-(5-pyridin-3-yl-thiophen-2-ylmethyl)aminorethyl]-2-(3,5-dimethylphenyl)-1H-indole-5-carboxylic acid diisopropylamide

Step 2A *N,N*-Diisopropyl-4-nitrobenzamide

A solution of 3.51 mL (2.53 g, 25 mmol) of diisopropylamine and 3.62 mL (2.63 g, 26 mmol) of triethylamine in 50 mL of anhydrous tetrahydrofuran was stirred under nitrogen and maintained at -5°C as a solution of 4.11 g (22.1 mmol) in 10 mL of anhydrous tetrahydrofuran was added dropwise over 15 minutes. The mixture was allowed to warm gradually to room temperature. After 2 hours, the mixture was filtered, and the filtrate was partitioned between diethyl ether and 1 N hydrochloric acid. The organic phase was then washed with saturated sodium carbonate₃ solution, then dried over sodium sulfate and filtered. The filtrate was concentrated *in vacuo*, and the residue was flash-chromatographed on silica gel (gradient elution with 2-5% MeOH in CH₂Cl₂) to yield 4.77 g (86%) of yellowish crystals, mp 141.5-142 °C; homogeneous by TLC 2:1 hexane-EtOAc. 500 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure.

Step 2B 4-Amino-*N,N*-diisopropylbenzamide

A mixture of 4.70 g (18.8 mmol) of *N,N*-diisopropyl-4-nitrobenzamide, 200 mg of 10% palladium on carbon, and 200 mL of 2-methoxyethanol was shaken with hydrogen at approx. 50 psig for 6.5 hours. The catalyst was removed by filtration through diatomaceous 5 earth under nitrogen. Concentration of the filtrate *in vacuo* afforded a quantitative yield of a yellow solid, mp 169.5-170 °C; homogeneous by TLC in 95:5 CH₂Cl₂-MeOH. 500 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure. Mass spectrum (PB-NH₃/CI): m/e = 221 (M + H).

10

Step 2C 4-Hydrazino-*N,N*-diisopropylbenzamide

Treatment of 4.2 g (19 mmol) of 4-amino-*N,N*-diisopropylbenzamide with 15 mL of concentrated hydrochloric acid and 10 mL of water was followed by agitation. The resulting solution was 15 maintained at approx. -3°C as a solution of 1.32 g (19.1 mmol) of sodium nitrite in 9 mL of water was added dropwise. After being stirred for an additional 30 minutes at this temperature, this solution was added portionwise to a vigorously stirred solution of 15.1 g (66.7 mmol) of stannous chloride dihydrate in 15 mL of concentrated hydrochloric acid, 20 which was maintained at about -10°C. After completion of the addition, the mixture was stirred at this temperature for 5 minutes and then allowed to warm to room temperature. At this point, it was again cooled and basified by gradual addition of 25 mL of 50% sodium hydroxide. The resulting precipitate was collected on a filter and partitioned between 25 tetrahydrofuran and 5 N sodium hydroxide in a 2:1 ratio. The aqueous layer was extracted 3 times with tetrahydrofuran. The combined organic fractions were concentrated *in vacuo*. The residue was taken up in CH₂Cl₂-EtOAc, dried over sodium sulfate, filtered, and reconcentrated to give 3.55 g (80%) of semisolid; homogeneous by TLC in 95:5 30 CH₂Cl₂-MeOH. 500 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure. Mass spectrum (PB-NH₃/CI): m/e = 236 (M + H).

Step 2D 3-(2-Aminoethyl)-2-(3,5-dimethylphenyl)-1*H*-indole-5-carboxylic acid diisopropylamide

A solution of 3.51 g (14.9 mmol) 4-hydrazino-*N,N*-diisopropylbenzamide (from Step 3) in 18 mL of 2-methoxyethanol was stirred at 100°C under nitrogen as 3.77 g (17.8 mmol) of 3-chloropropyl 3,5-dimethylphenyl ketone in 7 mL of 2-methoxyethanol was added

5 dropwise over 20 minutes. The solution was stirred at this temperature for 5 hours, then cooled and filtered to remove a solid (a tetrahydro-pyridazine by-product). The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (elution with 95:5 CH₂Cl₂-MeOH followed by a gradient of 98:2:0.2 to 92:8:0.8 CH₂Cl₂-MeOH-concd. NH₄OH) gave 1.78 g (31%) of a brownish, stiff foam; satisfactory purity by TLC in 95:5:0.5 CH₂Cl₂-MeOH-concd. NH₄OH. 500 MHz ¹H NMR (CDCl₃) was consistent with the assigned structure. Mass spectrum (PB-NH₃/CI): m/e = 392.2 (M + H).

10

15 Step 2E 3-[2-[Bis-(5-pyridin-3-yl-thiophen-2-ylmethyl)amino]ethyl]-2-(3,5-dimethylphenyl)-1*H*-indole-5-carboxylic acid diisopropylamide

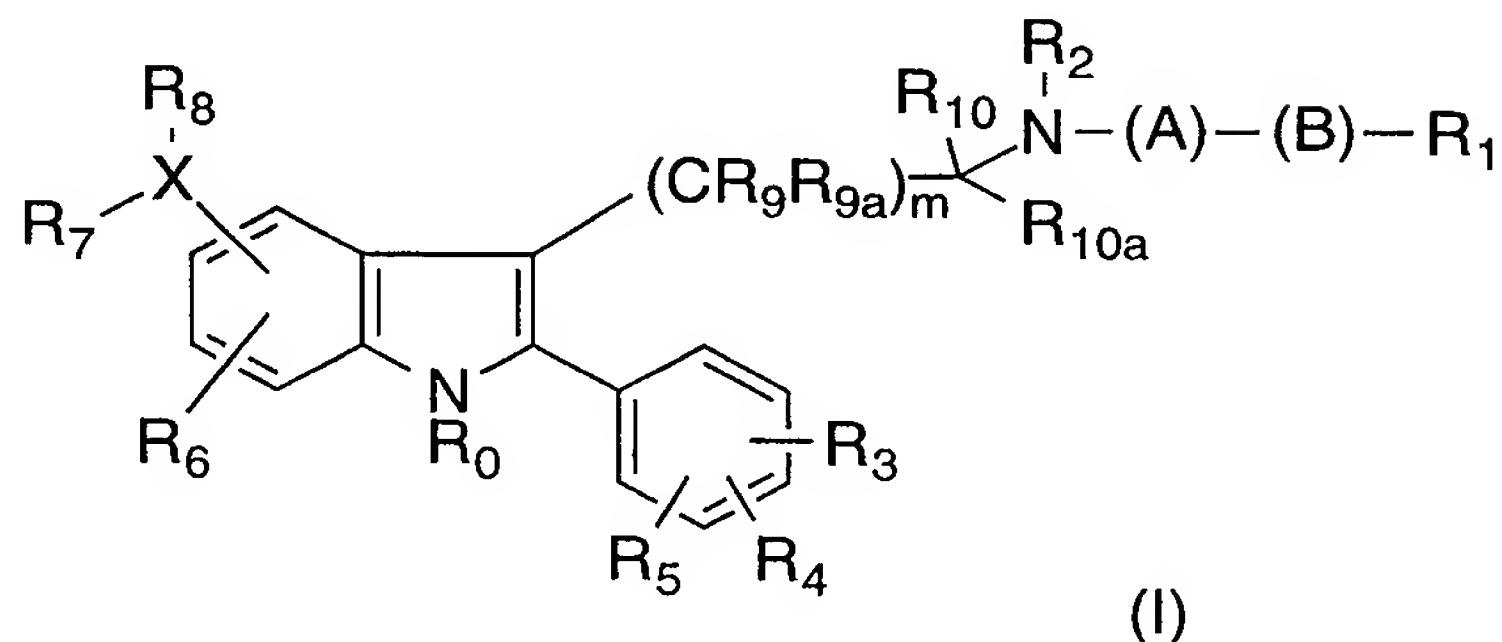
To a solution of 3-(2-aminoethyl)-2-(3,5-dimethylphenyl)-1*H*-indole-5-carboxylic acid diisopropylamide in a mixture of dry chloroform and methanol at 0°C is added magnesium sulfate followed by 2.5 equivalents of 5-pyridin-3-yl-thiophene-2-carbaldehyde and the mixture stirred at low temperature. After 40 minutes, acetic acid is added followed by a solution of sodium cyanoborohydride and the mixture allowed to warm to room temperature. After completion, the reaction

20

25 is quenched by the addition of saturated aqueous sodium bicarbonate, extracted with methylene chloride and the combined organics washed sequentially with water and brine. Purification of the concentrate by preparative tlc on silica gel gives the title compound.

WHAT IS CLAIMED IS:

1. A compound of the formula



5

wherein

A is R22-[heteroaryl]-R22- or R22-[substituted heteroaryl]-R22-;

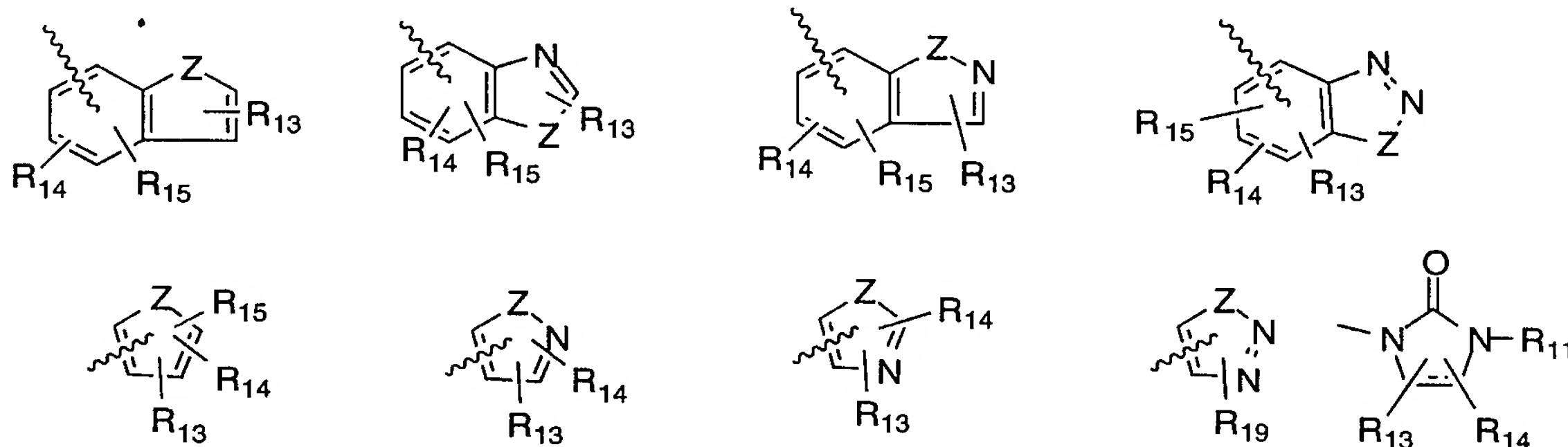
B is optionally absent, -OR22-, -C(=O)R22-, -S(O)nR22-,

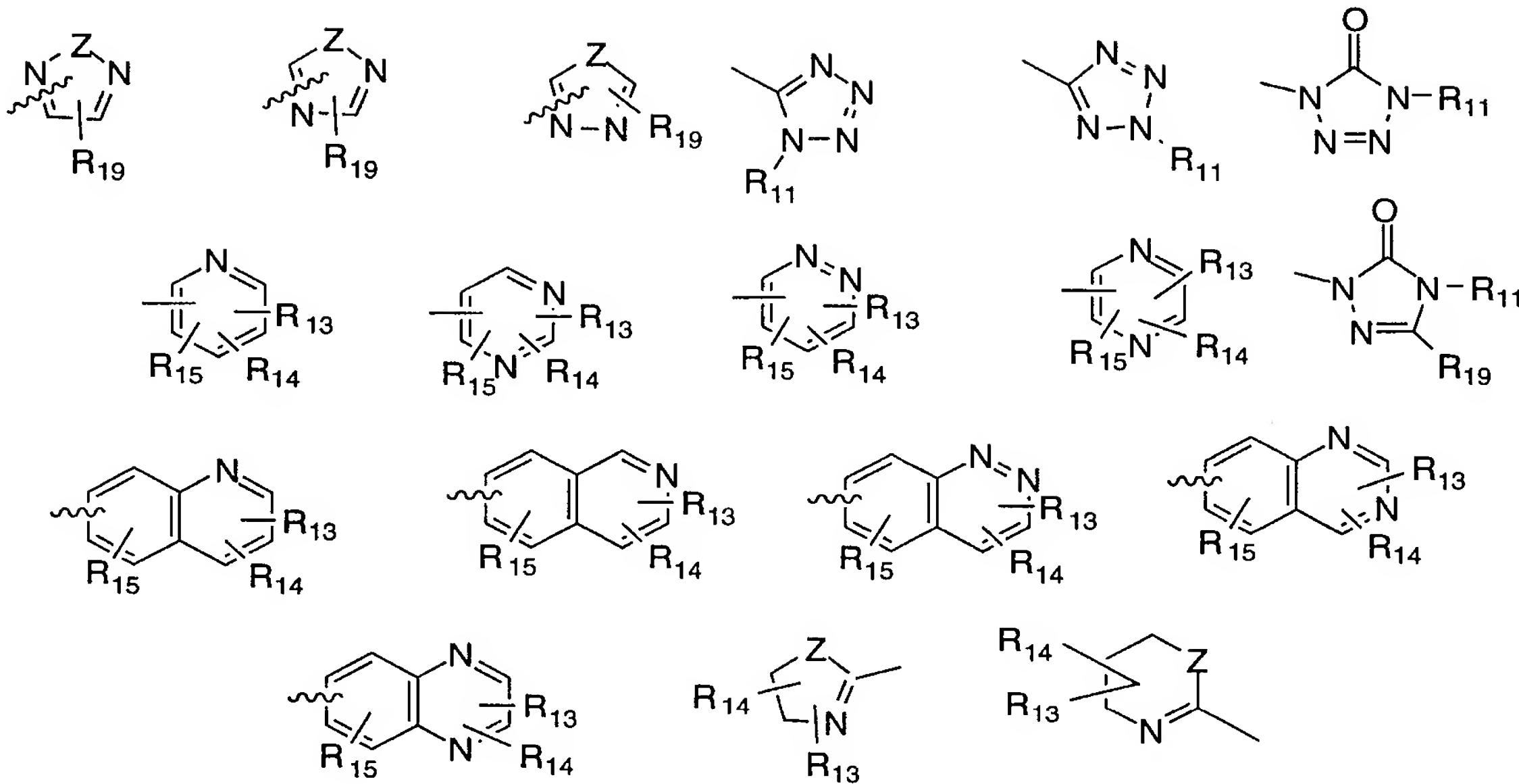
-NR18R22-, -OC(=O)R22-, -C(=O)OR22, -OS(O)nR22- or

-S(O)nOR22-;

10 R0 is hydrogen, C1-C6 alkyl, substituted C1-C6 alkyl, wherein the substituents are as defined below; aryl, substituted aryl, aralkyl or substituted aralkyl, wherein the substituents are as defined for R3, R4 and R5;

15 R1 is





the nitrogen atoms contained in the R₁ heteroaromatic rings may exist either as drawn or, when chemically allowed, in their oxidized (N→O) state;

5 R₂ is heteroaryl, substituted heteroaryl, C₁-C₆ heteroaralkyl, C₁-C₆ substituted heteroaralkyl; or

10 R₂ is A-B-R₁; or

R₂ and A can optionally be taken together to form a ring of 5-7 atoms;

15 R₃, R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, CN, nitro, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, aryl, substituted aryl, aralkyl, substituted aralkyl, R₁₁O(CH₂)_p-, (CH₂)_pS(O)_nR₁₇ or halogen; wherein R₁₇ is hydrogen, C₁-C₆ alkyl, C₁-C₃ perfluoroalkyl, aryl or substituted aryl; or

C₁-C₆ alkyl, C₁-C₃ perfluoroalkyl, aryl or substituted aryl; or

20 R₃ and R₄ taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing 1-3 heteroatoms selected from N, O and S;

R₆ is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, C₁-C₃ perfluoroalkyl, CN, NO₂, halogen, R₁₆O(CH₂)_p;

R7 is hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl, unless X is hydrogen or halogen, then R7 is absent;

R8 is hydrogen, C(O)OR₉, C(O)NR₁₁R₁₂, NR₁₁R₁₂, C(O)R₁₁, NR₁₂C(O)R₁₁, NR₁₂C(O)NR₁₁R₁₂, NR₁₂S(O)₂R₁₁, NR₁₂S(O)₂NR₁₁R₁₂, OC(O)R₁₁, OC(O)NR₁₁R₁₂, OR₁₁, SO_nR₁₁, S(O)_nNR₁₁R₁₂,, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅, C₁-C₆ alkyl or substituted C₁-C₆ alkyl, unless X is hydrogen or halogen, then R8 is absent; or

5 R7 and R8 taken together form a heterocyclic ring containing one or more heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅; or

10 R7 and R8 taken together form a carbocyclic ring of 3-7 atoms or when m≠0;

15 R9 and R9a are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl; aryl or substituted aryl, aralkyl or substituted aralkyl when m≠0; or

20 R9 and R9a taken together form a carbocyclic ring of 3-7 atoms or when m≠0;

R10 and R10a are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl; or

25 R10 and R10a taken together form a carbocyclic ring of 3-7 atoms or ; R9 and R10 when taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms when m≠0; or

R9 and R₂ taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms when m≠0; or

30 R10 and R₂ taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

15 R₁₁ and R₁₂ are independently a bond, hydrogen , C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic ring of 3-7 atoms, a substituted carbocyclic ring containing 3-7 atoms, a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅, C₁-C₆-alkyl substituted by a heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅;

10 R₁₁ and R₁₂ when taken together can form an optionally substituted ring of 3-9 atoms;

15 R₁₃ is hydrogen, OH, NR₇R₈, NR₁₆SO₂(C₁-C₆ alkyl), NR₁₆SO₂(substituted C₁-C₆ alkyl), NR₁₆SO₂(aryl), NR₁₆SO₂(substituted aryl), NR₁₆SO₂(C₁-C₃ perfluoroalkyl); SO₂NR₁₆(C₁-C₆ alkyl), SO₂NR₁₁(substituted C₁-C₆ alkyl), SO₂NR₁₁(aryl), SO₂NR₁₆(substituted aryl), SO₂NR₁₆(C₁-C₃ perfluoroalkyl); SO₂NR₁₆(C(O)C₁-C₆ alkyl); SO₂NR₁₆(C(O)-substituted C₁-C₆ alkyl); SO₂NR₁₆(C(O)-aryl); SO₂NR₁₆(C(O)-substituted aryl); S(O)_n(C₁-C₆ alkyl); S(O)_n(substituted C₁-C₆ alkyl), S(O)_n(aryl), S(O)_n(substituted aryl), C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, C₁-C₆ alkoxy, substituted C₁-C₆ alkoxy, COOH, halogen, NO₂ or CN;

20 25 R₁₄ and R₁₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, CN, nitro, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, aryl, substituted aryl, aralkyl, substituted aralkyl, R₁₆O(CH₂)_p-, R₁₆C(O)O(CH₂)_p-, R₁₆OC(O)(CH₂)_p-, -(CH₂)_pS(O)_nR₁₇, -(CH₂)_pC(O) N(R₁₆)₂ or halogen; wherein R₁₇ is hydrogen, C₁-C₆ alkyl, C₁-C₃ perfluoroalkyl, aryl or substituted aryl;

30 R₁₆ is hydrogen , C₁-C₆ alkyl, substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a carbocyclic

ring of 3-7 atoms or a substituted carbocyclic ring containing 3-7 atoms;

5 R₁₈ is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C(O)OR₁₆, C(O)N(R₁₆)₂, C(O)R₁₆, S(O)_nR₁₆;

5 R₁₉ is either the definition of R₁₃ or R₁₄;

5 R₂₂ is C₀-C₄ alkyl, substituted C₁-C₄ alkyl;

10 X is N, O, S(O)_n, C(O), (CR₁₁R₁₂)_p, a single bond to R₈, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; when X is O, S(O)_n, C(O), or CR₁₁R₁₂ only R₈ is possible;

10 Z is O, S or NR₁₁;

10 m is 0, 1, 2 or 3;

10 n is 0, 1 or 2;

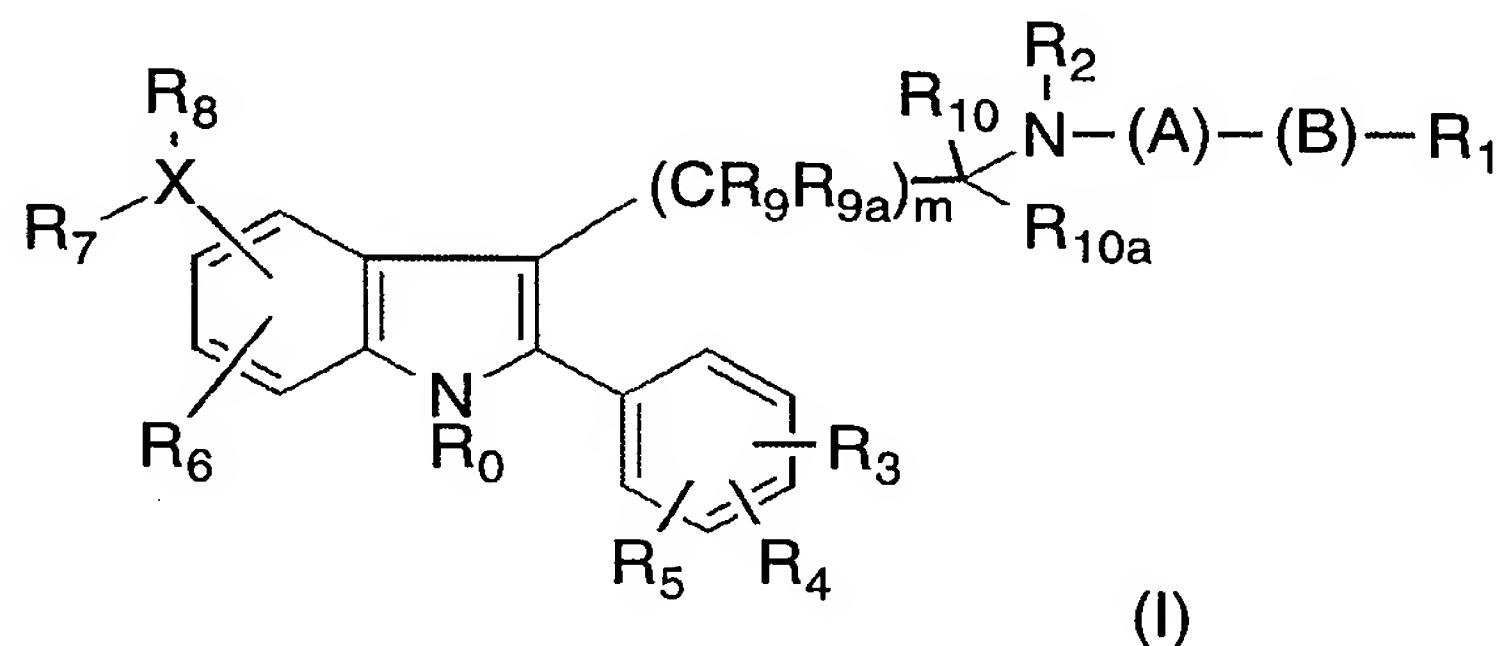
10 p is 0, 1, 2, 3 or 4; and

15 the alkyl, cycloalkyl, alkenyl and alkynyl substituents are selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, hydroxy, oxo, cyano, C₁-C₆ alkoxy, fluoro, C(O)OR₁₁, aryl C₁-C₃ alkoxy, substituted aryl C₁-C₃ alkoxy, and the aryl substituents are as defined for R₃,

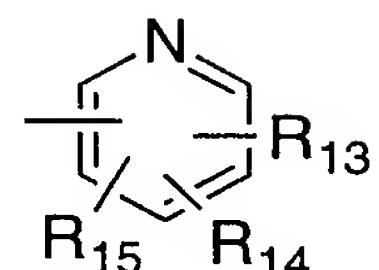
20 R₄ and R₅;

20 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

25 2. The compound according to Claim 1 of the formula



A is R₂₂-[thiophene]-R₂₂- ;
 R₀ is hydrogen;
 R₁ is



the nitrogen atoms contained in the R₁ heteroaromatic rings may exist either as drawn or, when chemically allowed, in their oxidized (N→O) state;

R₃, R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted

10 C₁-C₆ alkyl or halogen;

R₈ is C(O)NR₁₁R₁₂, or

R₁₁ and R₁₂ are independently a bond, hydrogen, C₁-C₆ alkyl,

substituted C₁-C₆ alkyl, aryl, substituted aryl, aralkyl,

substituted aralkyl, a carbocyclic ring of 3-7 atoms, a

15 substituted carbocyclic ring containing 3-7 atoms, a

heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4

heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅, C₁-C₆-alkyl substituted by a

heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4

20 heteroatoms selected from N, O or S which can be optionally substituted by R₃, R₄ and R₅;

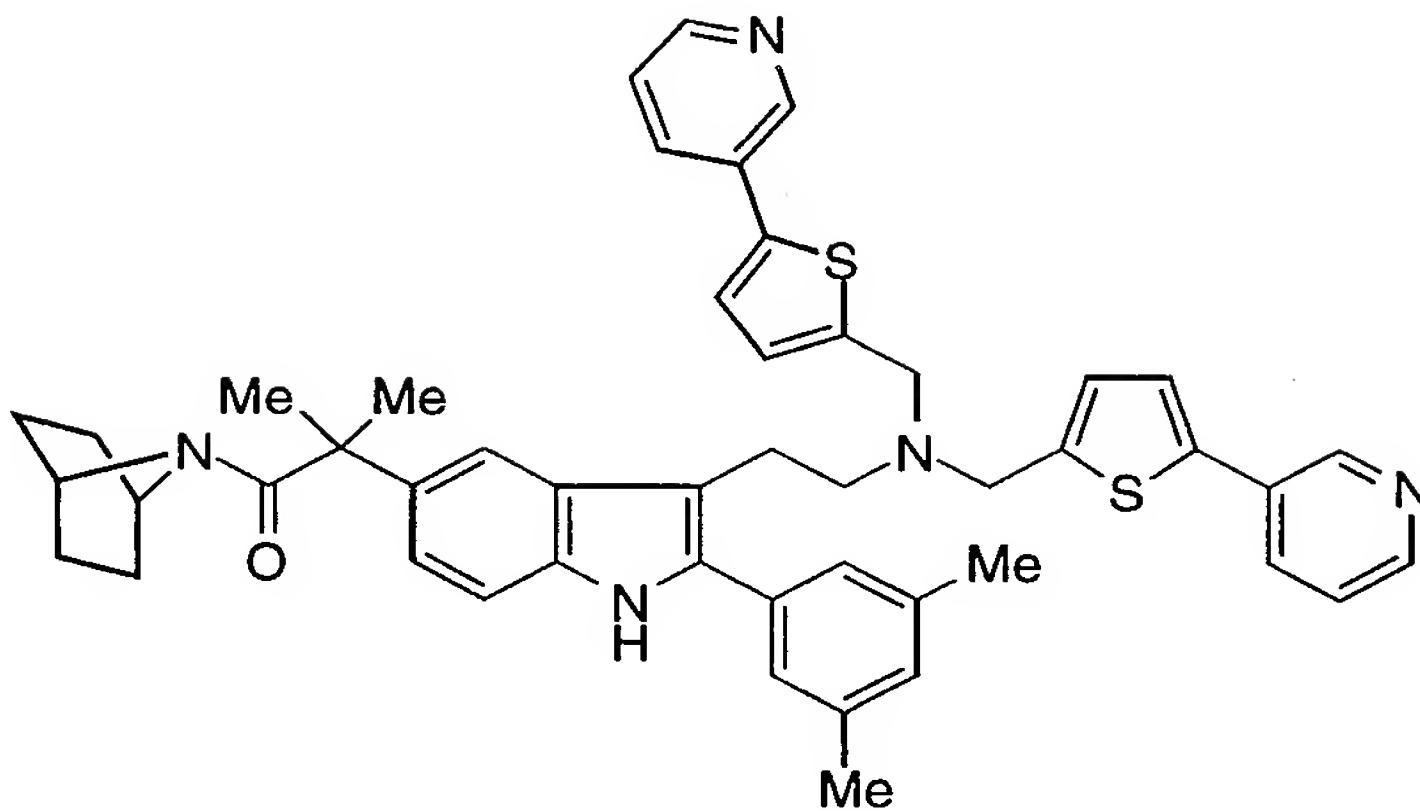
R₁₁ and R₁₂ when taken together can form an optionally substituted ring of 3-9 atoms;

X is (CR₁₁R₁₂)_p;

25 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

3. The compound according to Claim 1 of the formula

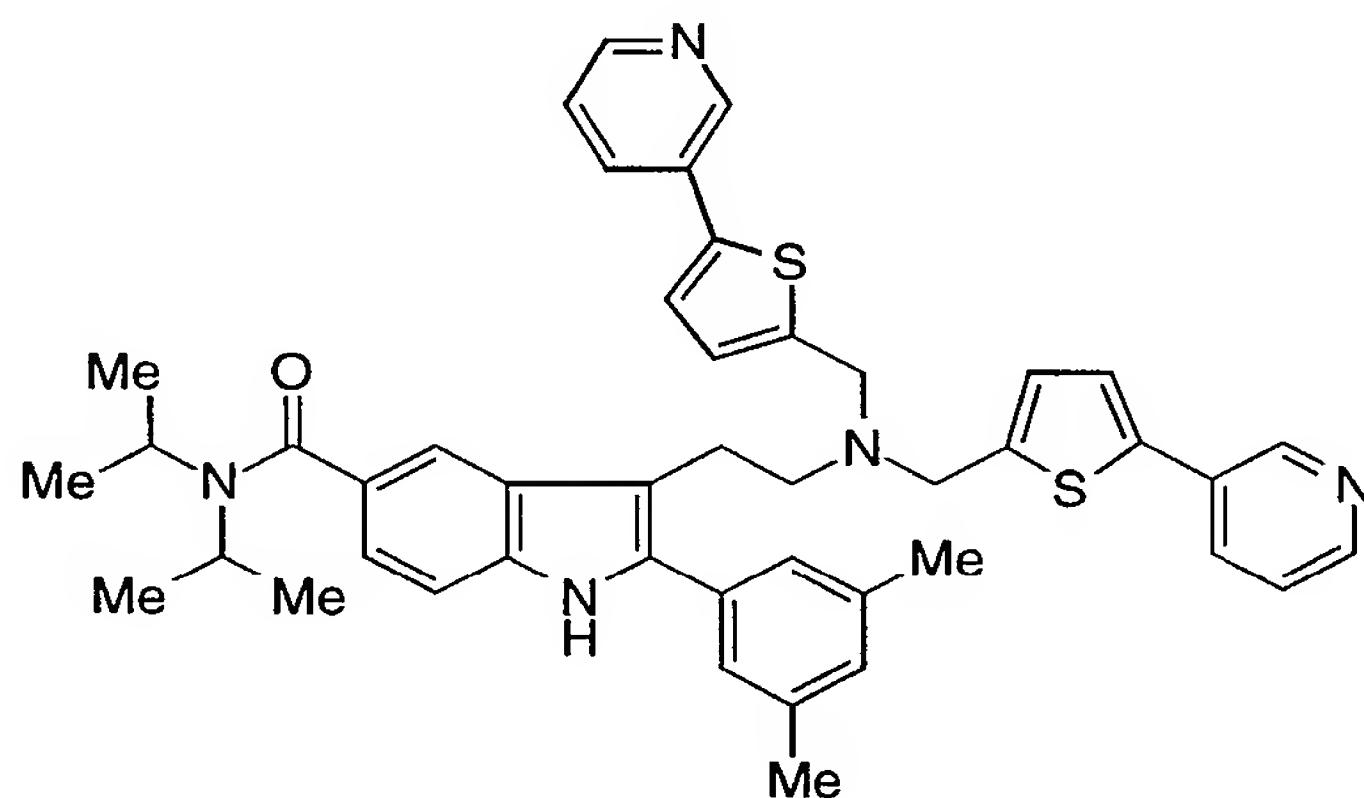
30



or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

5

4. The compound according to Claim 1 of the formula



10 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

15 5. A pharmaceutical composition which comprises an effective amount of a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

6. A method for antagonizing gonadotropin-releasing hormone in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1 to a subject suffering from a gonadotropin-releasing hormone derived disorder.

5

7. A method according to Claim 6 wherein the gonadotropin-releasing hormone derived disorder is a sex-hormone related condition.

10

8. A method according to Claim 6 wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent cancer, benign prostatic hypertropy or myoma of the uterus.

15

9. A method according to Claim 8 wherein the sex hormone dependent cancer is selected from the group consisting of prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenomas.

20

10. A method according to Claim 7 wherein the sex hormone related condition is selected from the group consisting of endometriosis, polycystic ovarian disease, uterine fibroids and precocious puberty.

25

11. A method for preventing pregnancy in a subject in need thereof which comprises administering an effective amount of a compound as defined in Claim 1.

30

12. A method for treating lupus erythematosis in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

35

13. A method for treating irritable bowel syndrome in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

14. A method for treating premenstrual syndrome in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

5

15. A method for treating hirsutism in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

10

16. A method for treating short stature or a growth hormone deficiency in a subject in need thereof which comprises administering to said subject an effective amount of a compound which stimulates the endogenous production or release of growth hormone and an effective amount of a compound as defined in Claim 1.

15

17. A method for treating sleep disorders such as sleep apnea in a subject in need thereof which comprises administering to said subject an effective amount of a compound as defined in Claim 1.

20

18. The method according to Claim 17 wherein the sleep disorder is sleep apnea.

25

19. A pharmaceutical composition which comprises an inert carrier and an effective amount of a compound which stimulates the endogenous production or release of growth hormone in combination with a compound as defined in Claim 1.

30

20. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier therefor.

21. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

35

22. A pharmaceutical comprising a compound having luteinizing hormone releasing hormone activity in combination with a compound of Claim 1.

5 23. The pharmaceutical of Claim 22 wherein the compound having luteinizing hormone releasing hormone activity is a peptide compound.

10 24. The pharmaceutical of Claim 23 wherein the peptide compound is a natural hormone or an analog thereof.

15 25. The pharmaceutical of Claim 23 wherein the peptide compound is a compound selected from the group consisting of leuprorelin, gonadorelin, buserelin, triptorelin, goserelin, nafarelin, histrelin, deslorelin, meterelin and recirelin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/11072

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 409/14; A61K 31/44

US CL :546/277.4; 514/339

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/277.4; 514/339

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P -----	WO 97/21703 A1 (MERCK & CO., INC.) 19 June 1997, see entire document.	1-25 -----
Y,P		1-25

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

13 AUGUST 1998

Date of mailing of the international search report

15 SEP 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

BRENDA COLEMAN

Telephone No. (703) 308-1235